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STUDIES ON THE URINARY EXCRETION AND BLOOD CONCENTRATION OF ASCORBIC ACID IN INFANTILE SCURVY

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INTRODUCTION

DURING the past year we have had the opportunity to study the excretion of ascorbic acid in the urine and to follow its concentration in the blood plasma in seven patients with active scurvy. The diagnosis of scurvy in this series of cases was based on the history of an inadequacy of vitamin C in the diet, the classical symptoms and physical signs, and the characteristic roentgenologic changes in the bones. Borderline cases have not been included in this study.

Before presenting the data in detail, it would seem to be of interest to review briefly the more important aspects of the investigations which have a bearing on this subject.

REVIEW OF LITERATURE

Although Harden and Zilva[1] inaugurated sustained and productive researches in 1918, aiming at the isolation of vitamin C, it was fourteen years later, in 1932, that King and Waugh[2] completed the isolation of the crystalline vitamin from a concentrate of lemon juice. This they identified as the hexuronic acid, produced from the adrenal cortex by St. Györgyi[3] during a series of brilliant studies on the function of peroxidase systems four years previously. One month after the appearance of King and Waugh's paper, Svirbely and St. Györgyi[4] announced that the hexuronic acid prepared in 1928 was an effective antiscorbutic and reported the Hungarian red pepper to be a rich source for the extraction of the crystalline material. They referred the study of the chemical structure of this substance, later to be renamed

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ascorbic acid on the continent and cevitamic acid in this country, to Haworth, Hirst and their coworkers at Birmingham. Independent investigations of the same nature were carried on by Reichstein in Zurich. Late in 1933 both laboratories[5, 6] announced successful syntheses from xylose, though the d-isomer of Reichstein proved inactive biologically, thereby establishing l-ascorbic acid, a lactone, to be vitamin C. Since then d-glucose has come to be the common source for the commercial synthesis of this material.[7]

Urine Studies.—Even before vitamin C was isolated its reaction with the dye, indophenol blue, introduced into biologic work by Clark and associates,[8] had been used to differentiate synthetic from natural fruit juices.[9] When the nature of this reaction was elucidated and the molecular structure of ascorbic acid determined, there was given to clinicians a laboratory test for the quantitative study of vitamin C nutrition. Van Eekelen and associates,[10] and Johnson and Zilva[11] investigated the urinary output of ascorbic acid in normal subjects on controlled ascorbic acid intake, and introduced the concept of vitamin C "saturation," a state of optimal ascorbic acid supply (maintained by some 50 mg. per day), above which excess vitamin C is excreted almost quantitatively (70 to 80 per cent) in the urine within eight hours of ingestion. This phenomenon has been confirmed by succeeding workers, although the status of ascorbic acid excretion during suboptimal intake, and during asymptomatic* and frank scurvy remains less clear. Harris and Ray[12] included studies on three scorbutic infants and observed a very low urinary response to a test dose of (100 mg.) ascorbic acid; they stressed the diagnostic value of this finding.

On the other hand, Johnson and Zilva[11] and Hawley and associates[13] have conclusively shown that unsaturated normal individuals may take 200 mg. doses of ascorbic acid for several days without significantly increasing the urinary output. The latter workers considered this fact "a serious limitation to the clinical use of the test suggested for the diagnosis of subclinical vitamin C deficiency."

Harris, Ray, and their coworkers[14] have recently reiterated the specific diagnostic value of urinary studies, and now advocate a test dose of 600-700 mg. ascorbic acid for adults—this despite the fact demonstrated by Johnson and Zilva that in fully saturated normal individuals large doses of this magnitude cannot be recovered in the urine in quantities much above 30 to 40 per cent of the amount ingested.

From the careful studies of Johnson and Zilva[11] and Van Eekelen[15] on their own vitamin C excretion over a sustained time interval it appears established that there is no further mechanism for ascorbic acid storage beyond saturation of the tissues. Thus every saturated individual placed on a scorbutic diet starts from scratch, so to speak,

*This term is used in preference to "subclinical scurvy" since the latter is capable of several definitions. It may be defined as an existing scurvy without characteristic symptoms, physical signs or roentgenologic evidences during life, but with histologic changes of early scurvy demonstrable at autopsy.

metabolizing a certain amount of his vitamin depot each day and excreting another portion prodigally, though on a decreasing scale in the urine. It is certain, moreover, that the longer individuals subsist on a scorbutic diet the larger are the amounts of vitamin C which are required to again effect saturation. Thus, Van Eekelen required some 1,800 mg. for resaturation after a month's abstinence from vitamin C-containing foods, although he had no signs of scurvy. Archer and Graham[16] showed that a similar amount was required to affect perceptibly the low level of urinary ascorbic acid excretion in a case of adult scurvy; still larger quantities were administered before saturation was reached.

Concerning the amount metabolized, Johnson and Zilva state that "the exploratory experiments performed with the object of ascertaining whether under certain conditions such as complete saturation and a suitable dose, the balance between the intake and the urinary excretion of ascorbic acid could possibly be utilized as a means of determining the daily requirements of the vitamin were disappointing" Notwithstanding, Harris, Ray and associates[14] have used this method and "calculating on a body weight basis and taking minimal and normal excretion values for a man of 10 stone" infer that the metabolic need of a 14-pound baby is in the neighborhood of 2.5 mg. per day. This is the equivalent of about a teaspoonful of orange juice, and judging from general clinical experience seems an extraordinarily low figure. It barely exceeds the minimal preventive dose for a 200-300-gram guinea pig.

Blood Studies.—Several investigators have studied ascorbic acid levels in the blood. Gabbe's values for serum[17] ranged from 0.14 to 1.21 mg. per cent for adults and he believed the differences could be explained by variations of vitamin C intake in the diet of his patients. Mirsky, Swadesh and Soskin[18] made plasma determinations in normal persons and those with chronic metabolic diseases. Their data are stated categorically, the normals ranging from 1.19 to 2.66 mg. per cent, and patients suffering with chronic diseases from 1.11 to 2.88 mg. per cent. Hawley and her associates[13] determined the ascorbic acid content of whole blood of 12 normal individuals and reported figures varying between 0.58 mg. per cent and 1.32 mg. per cent.

Abt, Farmer and Epstein[19] surveyed a large group of infants and children and concluded that "blood plasma values less than 0.75 mg. per cent to 0.80 mg. per cent of reduced cevitamic acid indicate a subnormal vitamin C intake." Thus they record determinations, which they consider subnormal, on fourteen subjects ranging from 0.769 mg. per cent to 0.513 mg. per cent.

There is general agreement then that the normal ascorbic acid content of the blood falls somewhere between 0.7 and 2 mg. per cent. The limits of subnormal zones, however, have yet to be elaborated. A blood ascorbic acid of 0.60 mg. per cent is lower than normal, but

where the level of suboptimal intake gives way to asymptomatic scurvy is the important feature if the test is to have any diagnostic value. In ten adult patients "with clinical manifestations of scurvy," reported by Taylor, Chase, and Faulkner,[20] the ascorbic acid content of the serum varied between 0.11 and 0.55 mg. per cent and averaged 0.245 mg. per cent.

The only cases of infantile scurvy reported to date in regard to blood ascorbic acid are two infants studied by Abt and Farmer who found initial plasma levels of 0.97 and 1.02 mg. per cent, with a rise of 2.01 and 2.08 mg. per cent, respectively, after the ingestion of but 160 mg. of the vitamin over a six-day period. Judging by the standards quoted above, and our experience with fifteen cases of scurvy, these figures are excessively high. The authors note that their "results should be taken as comparative rather than absolute values," and that subsequent estimations "indicate that these figures are probably too high."

This brings up the question as to the real significance of "absolute" values reported to date. They seem open to some doubt for the following reasons: vitamin C exists in relatively minute amounts in the blood; it is unstable and begins to undergo oxidation immediately after withdrawal[21]; from a purely physicochemical viewpoint, the titration of the 0.007 to 0.2 mg. ascorbic acid in 2 c.c. of normal serum or plasma is a procedure not without technical difficulties. Because of the dilution of the reagents and the time element necessary for the reaction, even the true end point of the titration with indophenol cannot be settled with exactitude. The several factors, catalytic and otherwise, which inhibit or facilitate such reactions are not completely clarified, and intensive studies of the sort done by Clark,[22] Barron, De Meio, and Klemperer[23] are needed for the solution of this problem.

METHOD OF STUDY

During the period of study, seven patients with scurvy were assigned to the metabolism room with special nursing facilities available. They were placed in metabolism beds, and accurate twenty-four-hour urine collections were made. At least two days were allowed to pass before therapy was instituted. During their hospital stay these infants remained on a maintenance diet of pasteurized milk and vitamin C-free soft solids.

The fasting content of ascorbic acid in the plasma was determined whenever possible. The following procedure based largely upon the work of authors already cited has been found the most satisfactory: 4 or 5 c.c. of blood drawn into a dry syringe is discharged gently to avoid hemolysis into an oxalate tube to which has been added a drop of 2 per cent potassium cyanide. Such a mixture can be kept several hours in the ice box since the cyanide inhibits any significant oxida-

tion of the vitamin.[23] The tube is centrifuged and 2 c.c. of plasma is withdrawn to another test tube. Four cubic centimeters of water is added and deproteinization accomplished by the addition of 4 c.c. of 5 per cent metaphosphoric acid. The mixture is stirred thoroughly with a glass rod, and filtered most quickly through a pleated paper. From the filtrate a 5 c.c. aliquot is taken for direct titration with 0.01 per cent indophenol. A 5 c.c. buret preferably graduated as fine as 0.01 c.c. with a similar sized drop is desirable. It is important that the technician accustom herself to an end point of a certain intensity,* and subtract a corresponding distilled water blank from the titration reading. All the reagents listed should be kept in the ice box and made up fresh not less than every two weeks. Standardization can be readily accomplished with a freshly weighed out ascorbic acid solution. The calculation† is based on the buret reading minus the blank times the dye factor (0.05 if pure and perfectly weighed out).

Urine specimens were measured as soon as passed and 10 to 20 c.c. samples acidified with 2 or 3 drops of glacial acetic acid and

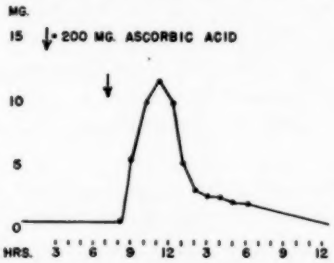

Chart 1.—Showing the hourly excretion of 64 mg. ascorbic acid in the urine after a 200 mg. dose, administered by mouth at 7:00 A.M. This chart has been reconstructed as accurately as possible from determinations on nine samples of urine, voided throughout a period of twenty-four hours by Patient 6 on the twelfth day of the experiment. The general character of the curve, which is somewhat diagrammatic because of the impossibility of obtaining evenly spaced samples, remains the same during periods of greater or lesser vitamin excretion, the peak being the main variable.

placed in an ice box. One or 2 c.c. were titrated with 0.02 per cent indophenol as soon after voiding as possible, although it would probably have sufficed to have done single determinations on the twenty-four-hour collections. In this way, however, more accurate information was gained concerning the time relationship of excreted ascorbic acid to its original ingestion (Chart 1). The blank for urine has been found slightly higher than for distilled water, and the end point somewhat obscured if larger quantities than 2 c.c. of a highly colored specimen are used.

*We have compared the accuracy of the end point as determined by the eye with that recorded by the photoelectric colorimeter (Evelyn[24]) where the depth of the color and rapidity of fading can be accurately observed. The comparison showed the agreement between the two methods to be so close that we use the more convenient method of direct titration with an observed end point.

†For details of the calculation the reader is referred to a discussion of the subject by Bessey and King.[25]

In all instances, the vitamin was administered as crystalline cebione (Merck) dissolved in several cubic centimeters of distilled water just before feeding and given with great care by teaspoon. Doses were usually in the neighborhood of 200 mg. and administered once or several times a day, depending upon the speed of saturation sought. Brief summaries of the case histories of these seven patients are given in the appendix to this paper.

In addition to the seven patients who were studied on metabolism beds, plasma determinations of ascorbic acid were made on eight other patients with active scurvy, subsequently admitted to the wards. For the purpose of securing control data, ascorbic acid values of the plasma were also studied in a group of fifteen unselected ward patients, and in a group of nine normal infants from a Well Baby Clinic.

RESULTS

Curves 1 to 6 (Chart 2) express graphically the results of this study in the individual cases. Each arrow indicates the ingestion of the specified dose of ascorbic acid. The solid dots represent the daily urinary excretion of ascorbic acid in milligrams, and the open circles represent the concentrations of plasma ascorbic acid in milligrams per cent. Time is plotted on the abscissas, and ascorbic acid on the ordinates.

Curve 1 shows the effect of supplying 1,000 mg. of the vitamin divided in equal doses over a ten-day interval. This infant was not on the metabolism bed during the period covered by the dotted line, but individual specimens titrated at that time showed no reducing power. In Curves 2 and 3 comparable end-results are demonstrable after the administration of approximately the same quantity of crystalline ascorbic acid in five 200 mg. doses within twelve hours and twenty-four hours, respectively. There is a definite lag observed in both of these curves, between the time when ascorbic acid is first recovered in the urine, and the time when a high level of excretion is reached. This is probably due to the fact that the administration of very large doses of the vitamin at the beginning of the experiment increased the blood levels out of proportion to tissue saturation with consequent spilling in the urine. In the subject depicted in Curve 4 there was a steady rise in the urinary excretion with the uninterrupted use of massive daily doses.

Curves 5 and 6 form an interesting comparison since the patients were both admitted to the hospital at the same time, and were treated side by side on practically the same regime. Although therapy was intended to be exactly parallel in these two cases, Patient 6 vomited half an hour after the first dose and, through an oversight, was given no vitamin on the third day. Patient 6 was by far the sickest infant

of the seven and was the only one to suffer from an acute nutritional disturbance which was manifested also in diarrhea and a continued oliguria. This condition finally necessitated his removal from the metabolism bed. It remains a matter of conjecture to account for

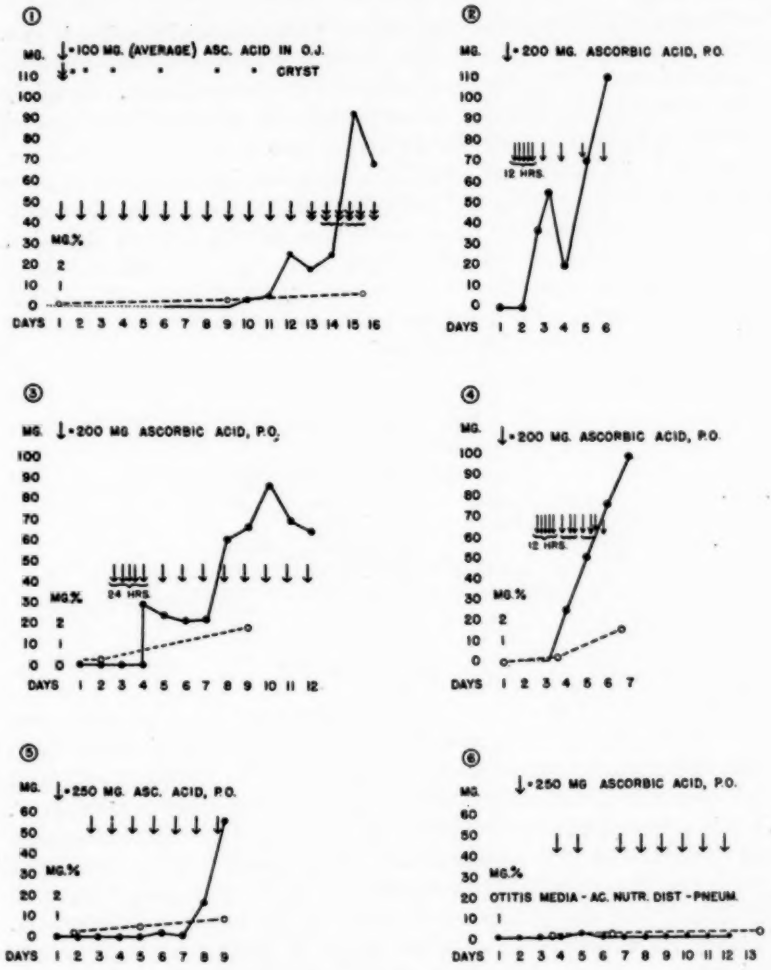

Chart 2.

the entire lack of response of this patient. The suggestion is that this failure was due to the marked metabolic disturbance just mentioned.

It is possible that the sudden drop of the vitamin excretion observed on the ninth day in Curve 7 (Chart 3) was due to otitis media which came into prominence about that time. On the other hand, it must

be kept in mind that most reported urinary studies on normal individuals occasionally show inexplicable variations in the urinary recovery of ascorbic acid administered as test doses, so that there is a definite hazard in drawing causal relationships from limited observations.

Generally speaking, the influence of complicating infection is particularly difficult to assay. Six of the seven patients suffered from upper respiratory infections of varying degrees of severity. Certainly the high ascorbic acid therapy alone did not seem to alleviate these disorders in anything like a specific manner.

Table I gives the ascorbic acid concentrations in the plasma of three groups of infants: first, well babies; second, babies picked at random from the ward; and third, patients with proved scurvy. The last group includes six of the seven patients studied on metabolism beds. No plasma ascorbic acid determinations were made on the seventh patient (Case 2). The ward cases are subdivided into two groups of higher and lower ascorbic acid values.

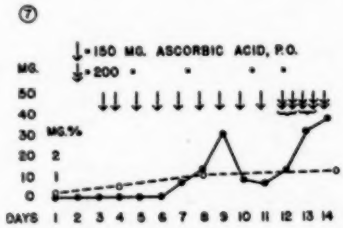

Chart 3.

DISCUSSION

The absence of ascorbic acid in the urine and the low plasma levels observed in the series of patients with active scurvy, together with the subsequent rises following therapy, are in disagreement with Rhomer and Bezssonoff's claim[25] that infants synthesize vitamin C. Their evidence was based on the continued excretion of ascorbic acid in the urine by two normal infants for forty-eight hours after they were placed on a vitamin C-free diet. Johnson and Zilva[11] and Van Eekelen[15] had also shown the inability of the kidney to retain completely the vitamin even when the subject is subsisting on a scorbutic dietary. Our data demonstrate that by the time frank clinical manifestations of the deficiency exist, the urine is depleted of ascorbic acid.

This urinary depletion has been shown before by Harris and Ray[12] and forms the basis of their use of test doses to demonstrate asymptomatic scurvy. However, the several stages of vitamin replenishment presented here have not been taken into consideration by them. It becomes apparent that test doses measure the degree of saturation, a

state so far removed from scurvy that the test becomes of questionable value as a purely diagnostic procedure. Our studies suggest that there are zones of ascorbic acid excretion in the urine generally characteristic of frank scurvy, asymptomatic scurvy, suboptimal and optimal intake.* What constitutes a level low enough to be characteristic of suboptimal intake, and when this merges into the lower level of asymptomatic scurvy, are phases still obscure.

We are in agreement with Johnson and Zilva that great caution should be used in interpreting results derived from urinary studies, particularly in attempting to measure the metabolic requirement by this method. We do, however, believe that very definite information has been gained from such studies. The concept of saturation has been valuable, and expresses one aspect of ascorbic acid nutrition never considered before the isolation of the vitamin. The urinary response to test doses has added more useful knowledge, especially in revealing that saturation is the exception rather than the rule for the great run of people. Moreover, it seems reasonable to state on the basis of the studies presented here that recovery from frank scurvy depends on the quantitative replenishment of ascorbic acid to the tissues through stages of absolute and then relative depletion, until an adequate depot has been attained. Hence, this may be accomplished quickly or over a longer period of time, depending primarily on the dosage.

We believe that greater emphasis should be given this quantitative aspect of ascorbic acid nutrition both in the prevention and treatment of scurvy. Thus, approximately 1,000 mg. or the equivalent of 2 liters of orange juice was required to affect perceptibly the absolute urinary depletion of the individuals in this series of cases. Each infant required about 2,000 mg. before even partial saturation was obtained. There is a tremendous discrepancy between these figures and the quantities of orange juice (averaging 0.5 mg. ascorbic acid per cubic centimeter) in common clinical use. Although it may be freely admitted that doses of the magnitude implied by our figures are unnecessarily high for recovery, nevertheless it seems probable that there has been a general tendency toward vitamin C underdosage in infancy, owing to neglect of viewing ascorbic acid supplements enough from the quantitative viewpoint. In addition to the amount of ascorbic acid needed for normal growth and function in infancy (estimated to lie between 15 and 30 mg. per day) there is suggestive evidence in the literature ([17, 26, 27]) and in our Cases 6 and 7 of an increased metabolic demand for ascorbic acid during certain morbid states.

*None of the infants here presented was carried to full saturation. An analysis of Harris and Ray's data indicates that their scorbutic patients though clinically cured were likewise only partially saturated.

TABLE I

	NO.	PLASMA ASCORBIC ACID MG. PER CENT	AGE (MO.)	SEX	ORANGE JUICE SUPPLEMENT	CLINICAL OBSERVATIONS	SCURVY BY X-RAY EXAMINATION
Well baby clinic	1	1.06	11	♂	Excellent*	Normal, healthy children under supervision of the Brookline Well Baby Clinic since infancy. The same nurse was in intimate contact with each patient of this group, and had supervised their dietary for many months.	
	2	1.32	10	♀	Excellent		
	3	1.30	13	♂	Excellent		
	4	0.45	13	♂	Excellent		
	5	0.80	14	♀	Excellent		
	6	0.92	12	♀	Excellent		
	7	0.93	16	♀	Excellent		
	8	1.11	15	♂	Excellent		
	9	1.07	16	♀	Excellent		
Average		1.00					
Babies picked at random from ward							
Higher values	1	0.61	17	♂	Adequate	Pharyngitis, bronchitis.	
	2	0.61	7	♂	Adequate	Constipation.	
	3	0.66	7	♂	Excellent	Bronchopneumonia.	
	4	1.05	23	♀	Adequate	Bronchopneumonia.	
	5	0.61	18	♀	Poor	Pyelonephritis.	
	6	1.10	14	♀	Adequate	Influenza.	
	7	0.73	13	♀	Adequate	Granulosa cell tumor.	
	8	0.94	18	♂	Excellent	Lobar pneumonia, epilepsy.	
	9	0.54	19	♀	? Adequate	Birth injury, cerebral defect.	
	10	0.49	22	♀	? Adequate	Lobar pneumonia, pediculosis.	
Average		0.73					
Lower values	1	0.28	13	♀	Poor	Pertussis 8 wk. Slight beading and Harrison's groove.	
	2	0.14	9	♂	None	Melena, intussusception, palpable beading.	
	3	0.38	7	♀	Poor	Hydrocephalus, hemiplegia, palpable beading.	
	4	0.05	9	♀	None	Acute nutritional disturbance, bilateral otitis. Sharp beading.	
	5	0.27	9	♂	Poor	Acute nutritional disturbance, healing rickets.	
Average		0.22					

* The writer wishes to express his gratitude to Miss Margaret Cushman for her assistance in the determination of many of the plasma ascorbic acid values listed in this table.

TABLE I—CONT'D

	NO.	PLASMA ASCORBIC ACID MG. PER CENT	AGE (MO.)	SEX	ORANGE JUICE SUPPLEMENT	CLINICAL OBSERVATIONS	SCURVY BY X-RAY EXAMINATION
Scorbutic ward patients							
(Case 1)	1	0.0+†	7	♂	Grossly inadequate	Pharyngitis, bronchitis, otitis.	+++
(Case 3)	2	0.08	7	♀	None	Nutritional anemia, cerebral deficiency.	+++
(Case 4)	3	0.0+	10	♀	None	Otitis, retarded development.	+++
(Case 5)	4	0.15	11	♀	Grossly inadequate	Intertrigo, impetigo.	+++
(Case 6)	5	0.05	9	♂	None	Nutritional anemia, otitis, upper respiratory infection.	+++
(Case 7)	6	0.15	9	♀	None	Nutritional anemia, otitis, upper respiratory infection.	+++
	7	0.0+	4	♀	Grossly inadequate	Nutritional anemia, rickets.	+++
	8	0.06	11	♂	None	Regulation of feeding.	+++
	9	0.0+	6	♂	None	Regulation of feeding.	+++
	10	0.0+	9	♀	Grossly inadequate	Bronchopneumonia, otitis	+++
	11	0.11	10	♂	Grossly inadequate	Regulation of feeding.	+++
	12	0.16	7	♀	Grossly inadequate	Rickets, pathological fracture neck of femur.	+++
	13	0.03	9	♀	Grossly inadequate	Rickets.	+++
	14	0.16	16	♂	Grossly inadequate	Chronic malnutrition.	+++
	15	0.10	13	♂	None	Marked rickets, acute scurvy, pneumonia.	None taken
Average		0.07					

*The prescribed dietary for these babies had included 2 ounces of orange juice a day for at least six months. A retrospect query concerning the habits of Patient 4 revealed a distaste for orange juice and an intake definitely lower than the prescribed 2 ounces.

†Too low to determine.

It would seem logical to suppose that saturation is the truly optimal state of ascorbic acid nutrition for the infant, since in the event of an increased demand or decreased supply, the vitamin depot is presumably larger than in partial saturation. However, it is certainly true also that normal health can be maintained at a lower level of supply. Further study is required to define more precisely the minimal protective dose for human beings. The time has come, however, when crystalline ascorbic acid can be used therapeutically in an effort to meet the quantitative metabolic demand if this is not supplied by fruit juices.

The results obtained in this study showed that the blood plasma of fifteen patients with the classical signs and roentgenologic evidences of scurvy contained an amount of ascorbic acid which averaged less than one-tenth of the values found in normal individuals. It is believed that with perfection of the method, ascorbic acid plasma determination will ultimately prove to be a diagnostic test by which it will be possible to detect the existence of scurvy in patients, before the appearance of the characteristic signs or roentgenologic changes, i.e., in borderline cases. Our material indicates a probable correlation of plasma values* for ascorbic acid with the nutritional state of the patient, which may be represented as given in Table II.

TABLE II

STATE OF VITAMIN C NUTRITION		PLASMA ASCORBIC ACID (MG. PER CENT)
Optimum	Saturation	2.00-1.00
	Normal	1.00-0.70
	Low normal	0.70-0.50
Suboptimum		0.50-0.30
Deficiency	Asymptomatic scurvy	0.30-0.15
	Scurvy	0.15-0

An analysis of the data obtained on the thirty ward patients, listed in Table I, suggested that ascorbic acid levels of the plasma are more closely related to vitamin C ingestion than to other influences such as infection. As pointed out previously, however, certain morbid states may possibly modify ascorbic acid metabolism, or hasten the onset of scurvy. Convincing evidence in this regard is very meager at present.

Finally, it is our feeling that, although studies of the blood and urine have a very important place in the clinical appraisal of vitamin C metabolism, the emphasis at present should be placed on correlation

*It is pointed out that these figures, though based upon experience to date, are somewhat arbitrary as the experimental error of the method is about 0.13 mg. per 100 c.c. Hence the sharp division of zones and their arrangement in even tenths of a milligram may create an impression of undue delicacy and finality. It is felt, however, that this scheme serves the purpose of summarizing existing data.

and analysis of the values found, rather than on the diagnostic implications of such data. These will be established only after a great deal more control material has been assembled and the chemistry of ascorbic acid metabolism is better understood. It is apparent that so many factors, including renal function, affect the urinary excretion of the vitamin, that the reducing power of the urine cannot be considered as a simple and reliable index of ascorbic acid nutrition.

SUMMARY

The excretion of ascorbic acid in the urine and its concentration in the plasma have been studied in seven cases of proved scurvy. Absolute depletion of ascorbic acid in the urine and very low values in the plasma were found. Vitamin replenishment was accomplished quickly or over a long period of time, depending primarily on the dose of ascorbic acid employed. In three groups of infants comprising well babies, babies picked at random from the ward, and patients with scurvy, concentrations of ascorbic acid in the plasma were demonstrated generally characteristic of optimal, suboptimal, and deficient intake of vitamin C. The limitations of the method and significance of results are discussed.

APPENDIX

CASE 1.—R. S., a seven-month-old boy, weighing 18 pounds 4 ounces, was brought to the hospital because of a generalized rash for three weeks prior to entry. Feeding was artificial with inadequate orange juice. Examination revealed slight cyanosis and widespread petechial hemorrhages of the skin. The gums were swollen and bleeding. There was beading of the ribs and the legs were swollen, tender and held in abduction. X-rays of the long bones showed advanced active scurvy. Laboratory studies revealed 15,700 white blood cells and 3,465,000 red blood cells per c.mm. The hemoglobin was 49 per cent. The urine showed no albumin. Microscopic examination of the urine revealed the presence of rare red blood cells.

On entry the patient exhibited such respiratory distress and cyanosis that the metabolism bed was out of the question for him. He was therefore kept on the ward during the period represented by the dotted line in Curve 1, Fig. 1, at which time urinary titrations were confined to single specimens. He was then transferred to the metabolism room. Treatment consisted of graduated daily doses of orange juice, averaging 100 milligrams ascorbic acid, over a twelve-day period. A change was then made to crystalline ascorbic acid and the dose doubled on the fourteenth and fifteenth days. The reducing properties of the blood and urine are expressed graphically in Curve 1. Discharge diagnoses included bronchitis, pharyngitis and otitis.

CASE 2.—M. J., a ten-month-old boy, weighing 18 pounds 2 ounces, was admitted to the Infants' Hospital because of inability for three weeks to use his legs. Feeding was artificial and orange juice was withheld because of a face rash. Examination revealed an apprehensive infant with swollen purplish gums. There was moderate beading of the costochondral junctions. The legs were drawn up on the abdomen and were painful when extended. X-ray films of the long bones showed moderately advanced active scurvy. The blood pressure averaged 100/65 with the baby quiet. There were 9,800 white blood cells and 6,590,000 red blood cells per c.mm. The hemoglobin was 59 per cent. The urine was clear without albumin.

After a two-day control period five doses of 200 mg. ascorbic acid were administered within twelve hours, and thereafter 200 mg. were given by mouth each morning. The urinary data are expressed in Curve 2, Fig. 1. Discharge diagnoses included upper respiratory infection and otitis.

CASE 3.—J. G., an eleven-month-old boy, weighing 20 pounds, was admitted to the Infants' Hospital because of irritability and tenderness of the legs for one month. He was one of twins. Birth was by breech extraction and bloody cerebrospinal fluid was detected by subdural tap shortly afterward. Orange juice had been refused constantly. Examination revealed marked irritability; swollen ecchymoses about the teeth, and a markedly angulated rosary. The knees were swollen and tender, and the legs held immobile. There was right facial weakness and Horner's syndrome was present. The blood pressure averaged 120/80 with the baby quiet. X-ray films of the long bones showed advanced scurvy. There were 6,800 white blood cells and 4,480,000 red blood cells per c.mm. The hemoglobin was 38 per cent. The urine was clear without albumin.

After a two-day control period five doses of 200 mg. ascorbic acid were administered within twenty-four hours, and thereafter 200 mg. were given by mouth each morning. The urinary data are expressed in Curve 3, Fig. 1. Discharge diagnoses included nutritional anemia, cerebral deficiency and hemiplegia.

CASE 4.—P. C., a ten-month-old girl, weighing 13 pounds 7 ounces, was admitted to the hospital with tenderness and immobility of the legs. One week before entry, bleeding of the gums was noted. The patient had been formula fed and consistently refused orange juice. Examination revealed a moderate number of gingival petechiae, a marked scorbutic rosary, and great tenderness of the legs which were held in abduction. X-rays of the long bones showed moderately advanced active scurvy. With the baby at rest, the average blood pressure was 125/80. There were 9,400 white blood cells and 4,250,000 red blood cells per c.mm. The hemoglobin was 65 per cent. The urine was clear without albumin.

After a control period of two days, 1,000 mg. ascorbic acid in five equally divided doses were administered by mouth during twenty-four hours. Thereafter 600 mg. ascorbic acid were given daily as expressed in Curve 4. Discharge diagnoses included otitis and retarded development.

CASE 5.—D. P., an eleven-month-old girl, weighing 17 pounds 2 ounces, was admitted to the hospital because of pain in the legs of two days' duration. Feeding was artificial. The orange juice supplement said to have been given to the baby daily had been carefully boiled by the mother. Examination revealed no disturbance of the gums. There was very slight costochondral beading. The left leg was markedly tender, swollen and held in a semiflexed position. X-ray films were characteristic of moderately advanced scurvy. The blood pressure was not recorded. There were 9,500 white blood cells and 4,940,000 red blood cells per c.mm. The hemoglobin was 50 per cent. The urine was clear without albumin.

After a control period of two days, 250 mg. of ascorbic acid were administered by mouth each morning. The reducing properties of the blood and urine are expressed in Curve 5. Discharge diagnoses included intertrigo and impetigo.

CASE 6.—W. W., a nine-month-old male infant, weighing 16 pounds 3 ounces, was admitted to the hospital at the same time as D. P. (Case 5), because of tenderness of the legs for three weeks. Feeding was artificial, and administration of an antiscorbutic had been neglected. The gums had been discolored for a month and the limbs very tender for two months. Examination showed injected, bulging eardrums; slight cough and snuffles; swollen ecchymotic gums; beaded, tender ribs; and immobile lower extremities. Roentgenograms showed moderately advanced active scurvy. The blood pressure was 100/65. There were 14,600 white blood cells and

4,900,000 red blood cells per c.mm. The hemoglobin was 57 per cent. The urine showed 1 or 2 red blood cells and occasional cellular casts per high power field. There was no albumin. Therapy in general paralleled that of the previous case. There was some vomiting one hour after the first dose of ascorbic acid, and through an oversight the daily dose was omitted on the third day. Nevertheless, the results plotted in Curve 6 form an interesting contrast to those shown in Curve 5.

The child's course on the metabolism bed was progressively downhill. He developed pneumonia, increased diarrhea, and finally, because of an acute nutritional disturbance, had to be removed from the conditions of the experiment. With transfusions and intravenous fluids and glucose, he recovered, although convalescence was prolonged.

CASE 7.—N. W., a nine-month-old girl, weighing 14 pounds 10 ounces, was admitted to the Infants' Hospital because of irritability of one month's duration. The child was artificially fed. Orange juice was said to have been vomited whenever tried. Examination revealed a few fading petechiae of the skin, normal gums, and a marked scorbutic rosary. The legs were swollen, tender and held in semiflexion. Roentgenograms showed changes of moderately advanced active scurvy. The blood pressure was 100/50. There were 8,300 white blood cells and 3,570,000 red blood cells per c.mm. The hemoglobin was 56 per cent. The urine was clear without albumin. After a two-day control period 150 mg. of ascorbic acid were administered daily for nine days, and thereafter 200 mg. doses as shown in Curve 7. Discharge diagnoses included nutritional anemia and upper respiratory infection.

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FULMINANT STREPTOCOCCIC SEPSIS IN INFANCY

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WHILE many organisms, notably the dysentery group, are capable of producing an overwhelming sepsis during infancy, the beta hemolytic streptococcus is the most common offender. Clinicopathologic contact with eight cases of a particularly lethal type of fulminating streptococcal infection in infants leads to this description of a fairly definite disease picture.

It is to be emphasized that this syndrome is of course but one of the many variations of streptococcic infection in early life. It is further apparent that all individuals suffering from septicemic infection with the beta hemolytic streptococcus do not die. The instances of acute sepsis described here differ primarily because death follows the onset of a bacteremia so quickly that localizing signs referable to individual organs rarely have time to appear. Septicemia of the newborn is not discussed.

ETIOLOGY

Although best exemplified in the premature infant, it is well established that all infants are especially susceptible to septic infection. In general, it has been held that this lower immunity of younger individuals may be explained by a combination of factors: the poor complement content of the serum, the weak antibody formation, the ready permeability of the skin and mucous membranes to living organisms, and the diminished defensive powers of the lymphatics.[1] More specific elucidation is to be found from some recent work of Lippard and Wheeler,[2] who show that the concentration of antifibrinolytic substance and the antistreptolysin titer of the blood diminish rapidly during the first few months of life, similar to that of other passively acquired immune bodies. They demonstrate further a minimal antistreptolytic and antifibrinolytic response to infection with hemolytic streptococci at this age.

An observation of interest and of some probable etiologic significance was the finding of active rickets among six of the eight infants upon which this contribution is based.

PATHOGENESIS

There are various portals of entry and modes of infection which are particularly characteristic of acute streptococcic sepsis, although the

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demonstration of a primary focus is not always possible. The most common atrium is through the pharynx and communicating cavities. Occasionally the organism may enter by way of the gastrointestinal or genitourinary tracts. As a rule, the disease becomes generalized without an intermediary lymphangitis or lymphadenitis. While pathologically interstitial infiltration of the lungs is an almost constant finding, the disease is not primarily a pneumonic process, but rather a widespread involvement of the entire body secondary to a bacteremia.

PATHOLOGY

There is a fairly well-defined uniformity in the pathologic changes observed in cases of this nature. Undoubtedly, the most important and typical feature is early bronchopneumonia of an interstitial type associated with peribronchitis. In addition, there is often an extensive cerebral edema without local cerebral lesions, and a diffuse edema of the optic nerves and spinal cord. Other common findings include petechial hemorrhages throughout the viscera, microscopic venous thrombi in the lungs and elsewhere, and "toxic changes" in the spleen and lymph nodes.[3] Culture of the heart's blood usually shows a growth of beta hemolytic streptococci, and in some cases the organisms are found in direct bacterial smears from the bronchi. The infection is of the pure septicemic type, and a typical pyemia with the development of metastatic abscesses seldom occurs. In rare instances there is evidence of terminal serous membrane involvement.

SYMPTOMATOLOGY

In a few cases, prior to the onset of apparent critical illness, a vague history of irritability, restlessness, refusal of food, and fever can be elicited. During this short prodromal stage occasional vomiting and mild diarrhea are frequently seen. More often, the infant is said to have been perfectly well until the sudden onset of his fatal illness.

When the disease is well established, there is commonly hyperpyrexia, meningism, profuse diarrhea, pharyngitis, and uncontrollable convulsions occurring singly or in combination, together with the usual manifestations of any severe infection. Petechiae of the skin may or may not be present, but icterus is rare. If debilitation is extreme, the course may be essentially afebrile. The following stories are quite typical:

CASE 1.—A native-born male infant, twenty-one months old, was seen after six hours of extensive convulsions. Birth had been normal, and his subsequent course was uneventful except for measles at thirteen months. On the preceding day a mild cough had developed. No illness was evident, although supper was refused that evening. At seven o'clock the following morning he was found in convulsions. Examination six hours later showed a well-developed and well-nourished infant in the throes of a generalized convulsion. There was moderate cyanosis, and his res-

pirations were shallow and stertorous with irregular periods of apnea. Other positive findings included a temperature of 105° F., rather marked pharyngeal injection, considerable neck rigidity, and hyperactive deep tendon reflexes. The lung fields were clear, and resonant throughout. Cerebrospinal fluid examination was negative except for some increase in pressure.

Therapy was unsuccessful, with death occurring two hours after examination and twenty-four hours following the development of initial symptoms. At necropsy, there was a diffuse infiltration of the pharynx and trachea, with an early streptococcal pneumonitis of the interstitial type. There was an associated edema of the brain with medullary pressure cone, acute splenitis, and cloudy swelling of the liver. Culture of the heart's blood showed a pure growth of beta hemolytic streptococci.

CASE 2.—A female infant, aged four months, was seen because of fever, diarrhea, and refusal of food for two days. The infant was thought to have been born two months prematurely and weighed 5 pounds at birth. She was breast fed, and no cod liver oil or substitute had been administered. Two days previous the infant became irritable and refused to nurse. Her temperature ranged from 100° to 103° F., and a profuse watery diarrhea developed. The mother was suffering from a sore throat. Upon examination an undernourished, dehydrated infant in extremis was found. The eyes were fixed, and there were numerous small petechiae over the abdomen and extremities. Craniotabes could be elicited. A pharyngitis and catarrhal otitis media were present. In the left axilla there were a few transitory showers of fine crackling râles with aeration and resonance unimpaired. Culture of the blood subsequently showed hemolytic streptococci. Roentgenograms of the wrist and chest were indicative of active rickets and peribronchial congestion, respectively. The baby's condition grew progressively worse, and death ensued seven hours later. At postmortem there was found a streptococcic bronchopneumonia and typical evidence of generalized septicemia.

Among this group of eight cases the duration of illness varied from twenty-four hours to six days, with an average duration of sixty hours. At other times death may occur with even more alarming rapidity. Farber, who feels that the streptococcus should be listed as one of the causes of sudden death in infancy, states that its killing effect is comparable to that of a powerful chemical poison.[3] He cites two instances of infants found dead a short time after having been put to bed in presumably perfect health. The strange circumstances and lack of history of previous illness led to an erroneous diagnosis of suffocation or of "thymic death" in each case. Autopsies showed overwhelming sepsis and hemolytic streptococci in the heart's blood.

DIAGNOSIS

From the protean symptomatology and paucity of specific physical signs, it is evident that the diagnosis of fulminating streptococcic sepsis is difficult. In the presence of a profuse diarrhea and neurologic manifestations the disease may be clinically indistinguishable from acute bacillary dysentery. Other cases presenting petechiae and meningismus are readily confused with meningococcic infection.

The age of greatest susceptibility is apparently from four to seven months. The determination of a pharyngitis or some other acute

focus in the upper respiratory tract suggestive of a portal of entry is significant. Not infrequently, a history of sore throat in another member of the household is obtainable. Associated rickets is frequently present. Whenever a critical illness is accompanied by convulsions uncontrolled by sedatives and the spinal fluid examination is negative, acute sepsis should be considered.

As might be anticipated, the interstitial pneumonia so often present, seldom gives rise to abnormal physical signs, for death intervenes before an appreciable amount of lung parenchyma has been involved. It is not until severe injury to the alveolar wall capillaries has occurred with resultant exudation of fluid and cellular elements into the alveolar spaces and bronchioles that râles can be elicited (Case 2). Roentgenograms are of no particular assistance.

While positive blood cultures offer the best confirmatory evidence, organisms are not invariably isolated from the blood, and the clinical picture should occupy first place in establishing diagnosis. In an embarrassing number this will unfortunately not be made until the cases come to autopsy.

SUMMARY

Based upon observations derived from contact with eight cases, a syndrome of rapidly fatal streptococcic sepsis in infancy is reported. Clinicopathologic characteristics of the infection are detailed together with etiologic and diagnostic considerations.

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A COMPARATIVE STUDY IN THE DIAGNOSIS AND TREATMENT OF RICKETS WITH OBSERVATIONS OF THE NORMAL AND ABNORMAL SERUM PHOSPHATASE

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THE questions of diagnosis, particularly as to degree, and of the treatment of rickets remain in an unsatisfactory state despite a considerable volume of work reported during the past few years. It seems unusual that the problem of diagnosis should still offer us difficulty; but, when we consider that the conclusions from blood chemical studies are largely based upon serum phosphorus determinations and upon the rapidity with which this particular component of the blood responds to antirachitic treatment, obviously, unless this determination represents the true picture of the activity of the disease, it may lead us into erroneous conclusions if it is used to measure degree and rate of healing. We may be relatively safe in concluding that an infant with a serum phosphorus of 4 mg. or less has active rickets. The converse of this, however, that an infant with a normal serum phosphorus does not have rickets, is often false. It would be equally misleading to assume that a rachitic baby whose serum phosphorus had risen from 4 mg. or less to normal was cured. Serum phosphorus determinations measure only the phosphate level of the blood, and that level, we well know, may be very rapidly altered under certain circumstances.

Roentgenologic diagnosis, the chief method now used in the diagnosis of rickets, also has very definite uncertainties and limitations. Early rickets, i.e., rickets which is developing but has not progressed to the point of showing density differences in the roentgenogram, is completely missed by x-ray examinations. When rickets is severe or even moderately advanced, the roentgenologic diagnosis is easy and should be quite accurate. The method has no quantitative scale to evaluate the degree of the involvement, and the disagreement between skilled observers as to the degree of involvement—whether healing is occurring or is completed, or whether the disease is active and progressing—may be tremendous. Sufficiently so that attempts to make certain quantitative comparisons on the basis of roentgenograms alone seem almost futile. It is true that an individual observer may agree quite closely in his own experiment, but, when we attempt to compare his findings with those of some other individual, we must recognize the inherent weakness of our position. Diagnoses of rickets

are expressed in terms of one-, two-, three-, or four-plus; or as mild, moderate, or severe; healed or healing; A1, A2, A3, or A4 degrees of activity, and perhaps in other ways. How are we to adjust these differences to a common basis for comparing different studies, particularly when we realize that for the milder forms of rickets, different individuals diagnosing the same series of roentgenograms may vary with one another in a high percentage of cases?

Attempts have been made to overcome this weakness in roentgenologic diagnosis[1] through the development of certain standards which by comparisons may help to estimate the calcium present and the vitamin D effects. At best, however, the methods represent indirect measurements in which the variable personal factor is large, and any direct, more accurate method which would permit the use of some mathematical standard would be of great assistance in evaluating our results.

Such a method seems now available through the determination of the blood serum phosphatase. Kay[2] has shown that in rickets the blood phosphatase is increased. Bodansky and Jaffe[3] more recently have reported studies of serum phosphatase in cases of active rickets. They felt that the phosphatase represented an excellent index of the activity of the disease and also that it was a measure of the healing which was taking place. Our own data, which were collected, with Bodansky's technic,[4] over a period of two winters, 1933-34 and 1934-35, led us to similar conclusions[5] with certain exceptions. We did not find, if sufficient vitamin D was used, that there was any "plateau" in our phosphatase curve as healing progressed. Neither were we quite certain from our blood and roentgenologic studies that, with the return of the serum phosphatase to normal, healing was completed. Perhaps the ability of the body to build normal bone was again restored, but complete restitution of lime salts, complete restoration to normal, as evidenced from x-ray examinations, often had not yet taken place.

An interesting result of our study was found in the comparison of our initial roentgenologic, blood chemical, and clinical diagnoses. All of the infants examined were from the Detroit Department of Health Child Welfare Clinics and were selected as probably having rickets on a basis of history of low or no vitamin D intake and the obvious presence of two or more of the commonly accepted physical signs of rickets. Complete data were obtained on 187 babies, and, according to careful x-ray diagnosis, only 50, or 26.7 per cent, had active rickets. If a serum phosphorus level of 4 mg. per cubic centimeter was accepted as the standard, then only 37, or 19.8 per cent, of the total had active rickets. Thus, in a group of welfare patients, all but a very few under one year of age and all selected as having active rickets on a basis of physical findings, our clinical success in diagnosis was only about 25

per cent as made from roentgenograms and 20 per cent according to serum phosphorus levels. If, however, serum phosphatase was taken as the criterion for judgment and the upper level of 12.5 mg. per cubic centimeter was accepted as normal range, then 123, or 65.8 per cent, had active rickets. It would appear that by the older methods of diagnosis we regularly miss a high percentage of active rickets in its early stages unless our diagnosis is made upon physical signs—signs which have been largely held unsatisfactory and which give us little evidence of degree of activity.

Since there is not available any large group of rachitic infants on which serum phosphatase studies have been made, we attempted from our data to select a range which would represent the normal. To obtain this, we grouped all the final blood phosphatase determinations from patients who had had, initially, normal roentgenograms, serum phosphorus of over 4 mg. per cubic centimeter, and at least thirty days of active treatment with 200, 300, 600, 800, or 1,000 Steenbock* units of vitamin D as cod liver oil concentrate. Of forty-two such infants the serum phosphorus of thirty-nine fell between 6 and 12.5 mg. (90.3 per cent). This was taken as representing a normal range for this group of infants, all of whom were two months or more old.

It was believed that, with a chemical method which offered a quantitative picture of the healing of rickets, further information might be obtained as to optimal amounts of vitamin D necessary in treating rickets. It was felt that healing should be as rapid as possible so that deformities could be kept at a minimum and the disturbed mineral metabolism could be restored to normal in the shortest time. With this in view, a group of 108 rachitic infants were observed clinically, roentgenologically, and with blood chemical studies. All showed clinical signs of the disease; some had abnormal roentgenograms; and all had some abnormality of the serum calcium, phosphorus, or phosphatase. They were divided into two main groups: Group A comprised fifty-nine patients who had serum phosphorus levels at 4 mg. per cubic centimeter or less, or with definitely active rickets and abnormally low serum calcium levels, there being only five with the latter. It was felt that, while the phosphatase findings might represent a better picture of the severity and progress of the disease, the older accepted standard of a low serum phosphorus should be used as the basis for selection. Group B comprised 49 infants whose serum phosphorus was higher than 4 mg. per cubic centimeter, but whose serums showed some other abnormality. These infants were consequently studied so that the effects of treatment upon the blood and roentgenograms could be further evaluated.

*The vitamin D assays of the cod liver oil concentrate were made in terms of Steenbock units. The factor generally used to multiply Steenbock units so that they will be converted into U. S. P. units is 2.7.

The two main groups were then divided into five groups each and were balanced according to serum phosphorus so that they were closely alike as regards severity of the disease. These five groups were then given a special experimental cod liver oil concentrate, prepared so that each group received levels of 200, 300, 600, 800, and 1,000 Steenbock units of vitamin D daily. This cod liver oil concentrate was

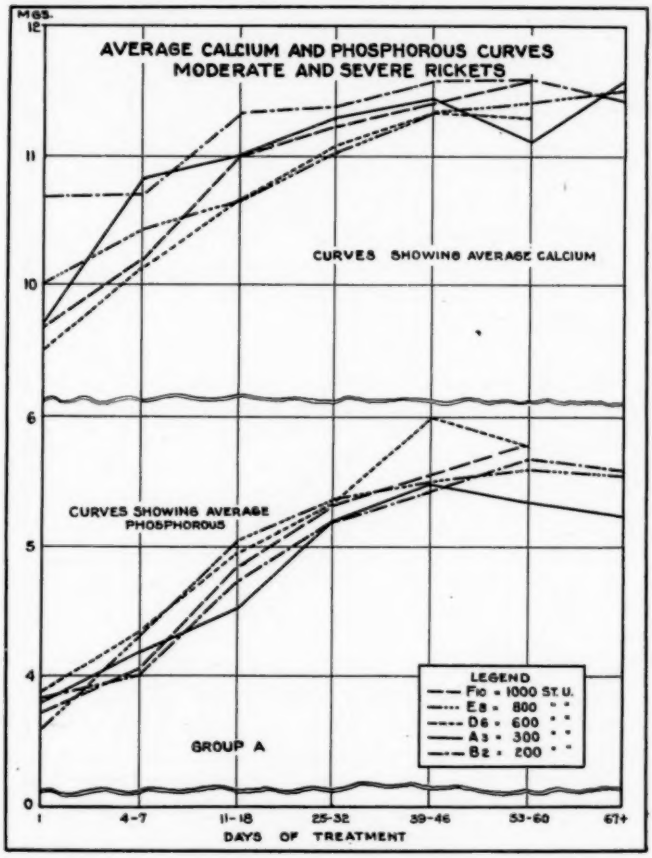

Chart 1.

assayed especially for the study and was given in doses of 10 drops per day by means of standardized pipettes.

In Group A, Table I, Charts 1 and 2, it is noteworthy that the average serum phosphorus had risen to above 4 mg. per cubic centimeter within from four to seven days and that the group receiving 200 Steenbock units of vitamin D per day showed the slightest gain. Also

that, while serum phosphorus of the rest remained below 5 mg. per cubic centimeter, that of the group given the 800 Steenbock units was above 5 mg. per cubic centimeter after eleven to eighteen days' treatment, although its initial level was slightly lower than the rest. All groups had normal phosphorus levels (above 5.4 mg. per cubic centimeter) after treatment of thirty-nine to forty-six days. It is also

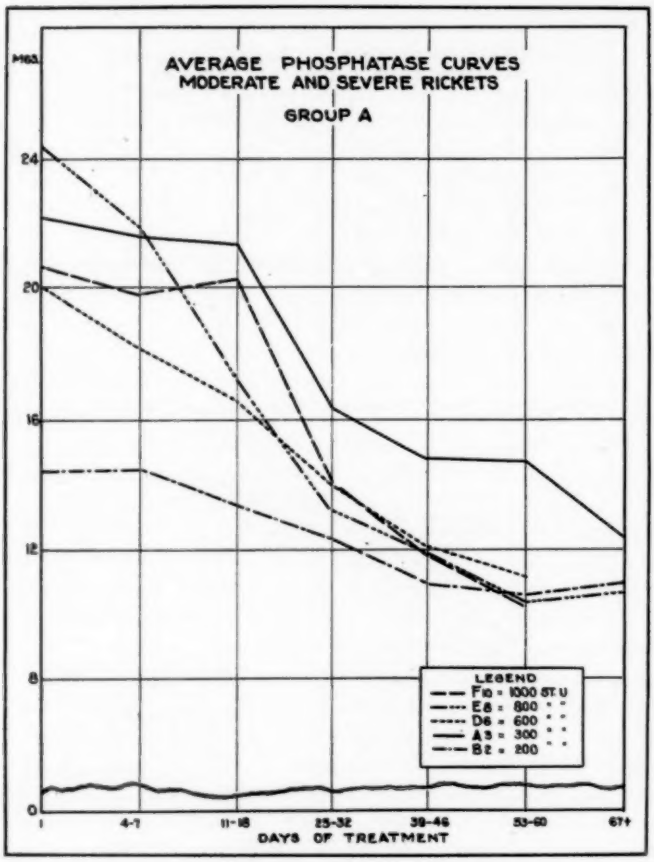

Chart 2.

evident that the groups receiving 600, 800, and 1,000 Steenbock units of vitamin D as cod liver oil concentrate regained normal serum phosphorus levels more rapidly than did the groups getting 200 and 300 units per day.

When we consider the average serum phosphatase findings, the same general results are apparent. There is somewhat more variation in the

initial average phosphatase content because case selection was on a basis of phosphorus rather than phosphatase. Particularly is this true in the results from the group given 200 Steenbock units which was not increased to the size of the others because of the fear that response to treatment was too slow.

TABLE I

GROUP A. MODERATE AND SEVERE RICKETS, SHOWING AVERAGE BLOOD CALCIUM, PHOSPHORUS AND PHOSPHATASE DETERMINATIONS DURING TREATMENT OF PATIENTS IN GROUP A

TREATMENT	INITIAL	4-7 DAYS	11-18 DAYS	25-32 DAYS	39-46 DAYS	53-60 DAYS	67 DAYS
Serum Calcium (Milligrams Per Cubic Centimeter)							
B-2	10.67	10.71	11.34	11.38	11.57	11.59	11.41
A-3	9.68	10.83	10.99	11.28	11.44	11.10	11.59
D-6	9.50	10.12	10.65	11.08	11.33	11.29	11.69
E-8	9.99	10.41	10.65	11.03	11.34	11.39	11.51
F-10	9.66	10.20	11.01	11.19	11.37	11.56	
Serum Phosphorus (Milligrams Per Cubic Centimeter)							
B-2	3.83	4.09	4.72	5.18	5.42	5.66	5.57
A-3	3.78	4.17	4.53	5.19	5.46	5.34	5.24
D-6	3.86	4.32	4.93	5.32	5.50	5.10	4.64
E-8	3.60	4.30	5.02	5.38	5.49	5.57	5.53
F-10	3.69	4.33	4.83	5.28	5.48	5.79	
Serum Phosphatase (Milligrams Per Cubic Centimeter)							
B-2	14.32	14.37	13.28	12.25	10.92	10.34	10.96
A-3	22.19	21.66	21.32	16.25	14.80	14.73	12.42
D-6	20.03	18.05	16.50	13.92	12.08	11.16	11.33
E-8	24.36	21.79	17.11	13.09	11.84	10.35	10.45
F-10	20.50	19.08	16.95	13.96	11.87	10.21	

B-2 represents 200 Steenbock units. Number of patients treated—8.
A-3 represents 300 Steenbock units. Number of patients treated—12.
D-6 represents 600 Steenbock units. Number of patients treated—11.
E-8 represents 800 Steenbock units. Number of patients treated—15.
F-10 represents 1,000 Steenbock units. Number of patients treated—13.

However, it is seen that with a daily dose of 200 Steenbock units of vitamin D, the average serum phosphatase content rose slightly after four to seven days' treatment, and with 300 Steenbock units per day there was a very gradual fall. On the other hand, in the infants given 600 and 800 Steenbock units per day, the drop in serum phosphatase was definite and marked. Peculiarly, the group given 1,000 Steenbock units per day showed a rise in serum phosphatase (average) after eleven to eighteen days' treatment. The fall was quite pronounced, however, after twenty-five to thirty-two days. With the groups receiving 600 and 800 Steenbock units per day, the rapidity of the fall of serum phosphatase levels after eleven to eighteen days of treatment was still maintained, and after twenty-five to thirty-two days of treatment the groups given 600, 800, and 1,000 Steenbock units per day were definitely lower than the group given 300 Steenbock units per day. The original low level of the group given 200

Steenbock units makes similar comparisons after twenty-five to thirty-two days of treatment unsatisfactory. The serum phosphatase of the group receiving 300 Steenbock units per day remained quite high, although figures for the rest were significantly lower and approached normal. After thirty-nine to forty-six days of treatment, all except the group receiving 300 Steenbock units had normal average phosphatase. It must be noted here (Chart 3) that the infants receiving 800 Steenbock units showed a return of serum phosphatase to normal at a rate significantly better than did the remainder. Also, the groups getting 600 and 1,000 Steenbock units of vitamin D per day as cod

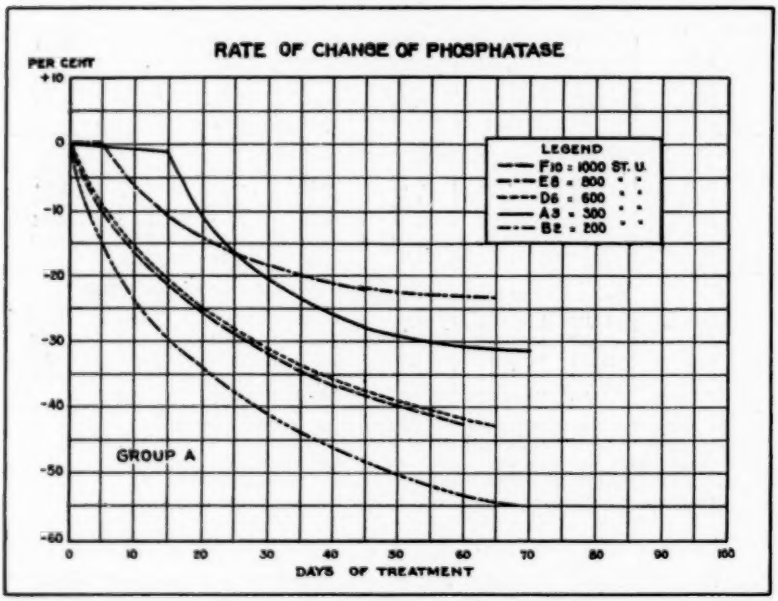

Chart 3.

liver oil concentrate paralleled each other closely, and their rates of change showed no significant difference. All three groups receiving 600, 800, and 1,000 Steenbock units were significantly better than those receiving 200 or 300 Steenbock units a day. In those patients receiving 200 Steenbock units of vitamin D per day, the rate of decline may have been influenced by the fact that the average phosphatase was initially lower than in the others. However, it is probably significant that it showed, as did the 300 Steenbock unit group, very little fall after four to seven days' treatment. In attempting to further test the relative value of the phosphatase determination as a measure of healing, the patients were divided according to initial

phosphatase readings: those up to 20 mg. per cubic centimeter and those from 20 mg. to 30 mg. per cubic centimeter. A curve was then drawn for the various dosage levels, showing the average fall per day of treatment. Such a procedure should minimize the errors present when the total group average phosphatase determinations are used. Some interesting differences are noted, although certain other observa-

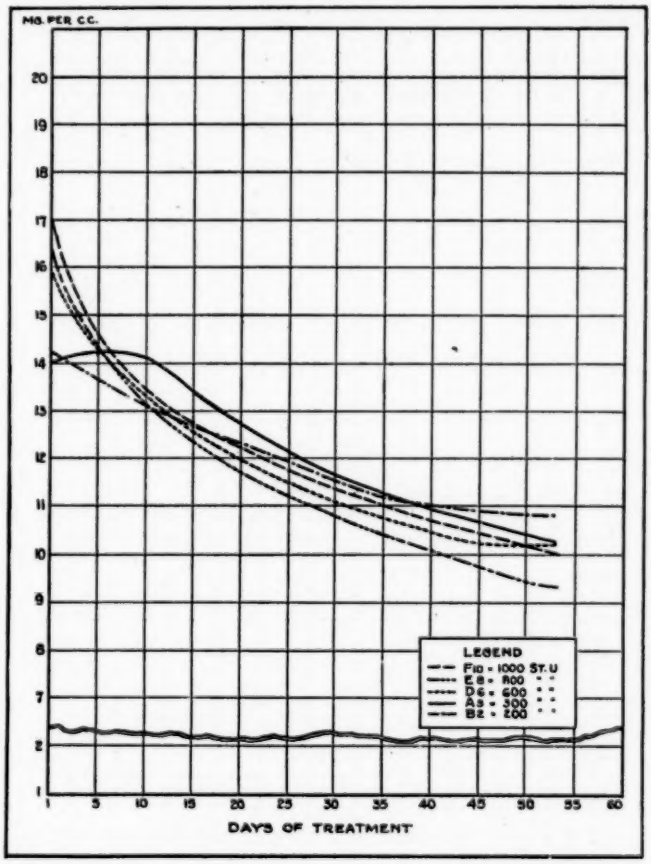

Chart 4.—Cases with initial phosphatase determinations of 6 to 20 mg. per cubic centimeter.

tions persist regardless of how the data are treated. Chart 4 consists of curves plotted from all the serum phosphatase determinations which initially fell between 6 mg. and 20 mg. per cubic centimeter. Here again the initial determinations for the groups given 200 and 300 Steenbock units were lower than the rest. They showed very little drop in from four to seven days, and in from eleven to eighteen days,

those of the 300 Steenbock unit group were even higher than initially. From then on, both gradually fell, coming within the upper normal range after twenty to twenty-three days of treatment, but approaching the lower normal range very gradually. The initial phosphatase content of the group given 600 Steenbock units per day fell definitely after four to seven days of treatment, and the rate of decrease continued

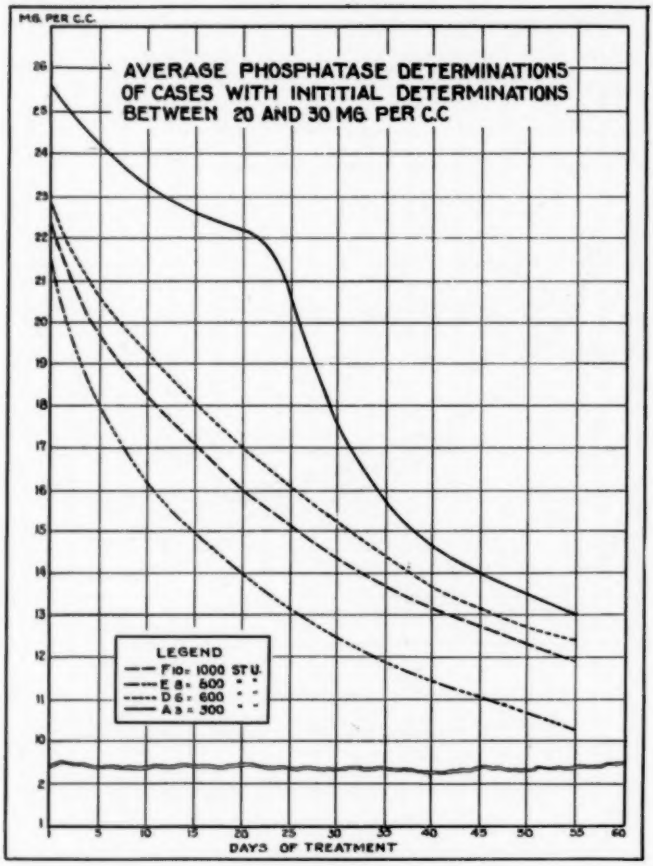
MG. PER C.C.
AVERAGE PHOSPHATASE DETERMINATIONS OF CASES WITH INITITIAL DETERMINATIONS BETWEEN 20 AND 30 MG. PER C.C
LEGEND
F = 1000 STU.
E = 600 " "
D = 600 " "
A = 300 " "
DAYS OF TREATMENT

Chart 5.

throughout the period of observation, though not as rapidly as that occurring in the group receiving 800 Steenbock units per day. From Chart 4 it is apparent, rate of recovery being measured by the phosphatase curve, that the 1,000 Steenbock unit group paralleled the 600 Steenbock unit group. In Chart 4, however, as in Chart 3, the phosphatase curve of the group receiving 800 Steenbock units per day showed the

quickest and most complete return to normal. This feature, it will be observed, follows throughout, regardless of how the problem is approached, and appears to represent a significant finding.

Two few infants with phosphatase determinations of 20 to 30 mg. per cubic centimeter received 200 Steenbock units per day to plot a satisfactory curve. However, in the other groups (Chart 5) the same trend is observed as in Chart 4. There was no rise in the phosphatase content in the 300 Steenbock unit group after eleven to eighteen days of treatment, but here again the group receiving 800

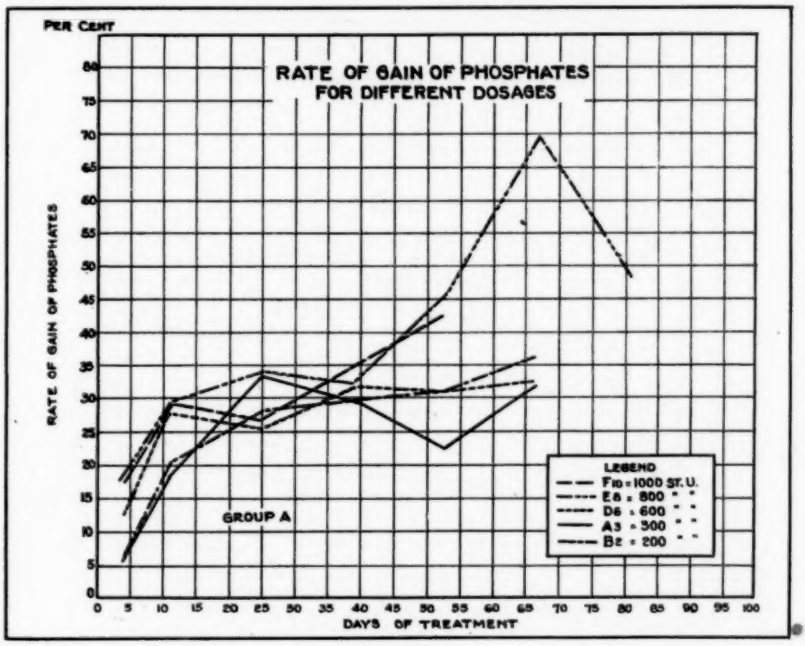

Chart 6.

Steenbock units was significantly the best, and the 1,000 and 600 Steenbock unit groups follow in that order. A more definite separation between the 600 and 1,000 Steenbock unit groups was apparent, the larger dosage seeming more effective. The curves suggest that 300 and 600 Steenbock units per day are less than the optimal healing dose, that 1,000 Steenbock units exceed it somewhat, and that 800 Steenbock units per day are most effective.

The same general condition holds for rate of change of phosphorus (Chart 6), and, as we can expect, the phosphorus responses of the groups

receiving 600 and 1,000 Steenbock units per day paralleled each other. Also, though all groups reached normal, the rates of change of the three receiving the largest doses were significantly greater than were those given but 200 and 300 Steenbock units per day, and here again the 800 Steenbock unit dosage seemed most effective.

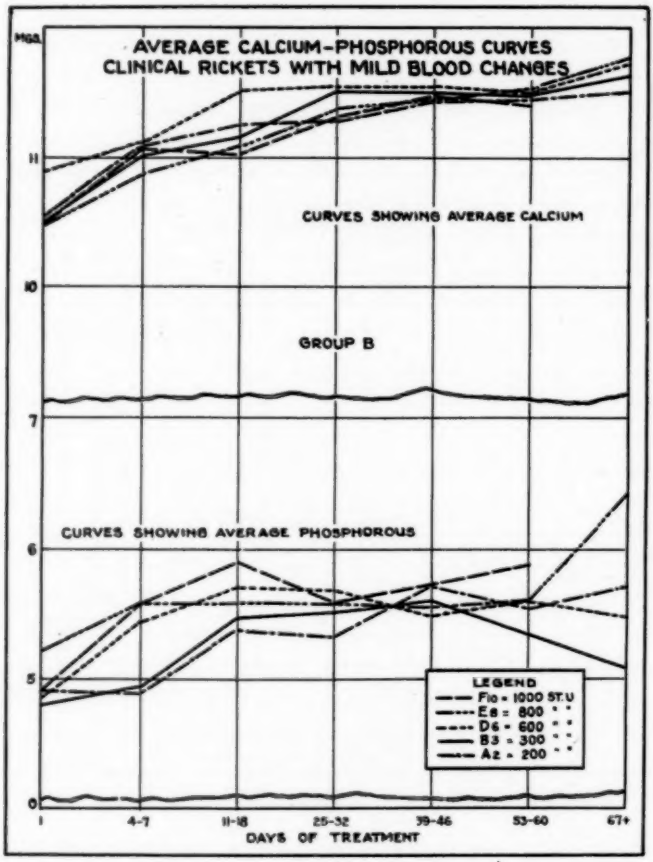

Chart 7.

Little need be said concerning the serum calcium levels. With the exception of the 200 Steenbock unit groups, the serum calcium contents all averaged low initially and rose promptly to normal by the eleventh to the eighteenth day.

Those patients showing sufficient clinical, roentgenologic, or blood abnormalities to warrant further observation, classified as Group B (Table II), followed quite closely the course of those who had definite

rickets at the start. The average calcium determinations (Table II and Charts 7 and 8) were within the normal limits at the start of treatment and increased with the administration of vitamin D. The initial average phosphorus determinations were slightly low but were promptly elevated with treatment. The serum phosphatase averages responded as expected, all averages having returned to normal by the twenty-fifth to the thirty-second day.

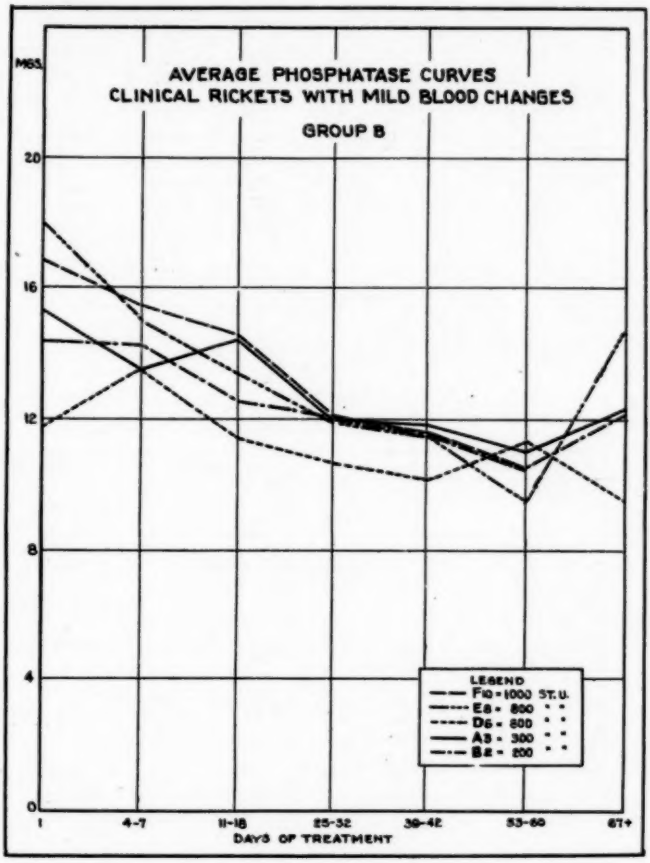

Chart 8.

Since it was felt that the presence of anemia considerably affected the progress of healing, during the second winter routine hemoglobin determinations and blood counts were made. The hemoglobin content was determined by the Haden-Hauser method and was expressed in grams of hemoglobin. One striking case was that of M. S. (Table III), who received 800 Steenbock units of vitamin D per day. This patient

Table II

Group B. Clinical Rickets With Mild Blood Changes, Showing Average Blood Calcium, Phosphorus and Phosphatase Determinations During Treatment of Patients in Group B

Treatment	Initial	4-7 days	11-18 days	25-32 days	39-46 days	53-60 days	67 days
Serum Calcium (Milligrams Per Cubic Centimeter)							
B-2	10.52	11.07	11.22	11.26	11.42	11.43	11.48
A-3	10.54	11.01	11.15	11.50	11.51	11.54	11.64
D-6	10.93	11.11	11.51	11.54	11.54	11.50	11.69
E-8	10.47	10.87	11.08	11.35	11.41	11.50	11.73
F-10	10.52	11.07	11.02	11.31	11.45	11.36	
Serum Phosphorus (Milligrams Per Cubic Centimeter)							
B-2	4.91	4.87	5.38	5.31	5.70	5.52	5.71
A-3	4.82	4.93	5.46	5.49	5.57	5.34	5.11
D-6	4.84	5.43	5.72	5.69	5.48	5.61	5.46
E-8	5.16	5.57	5.59	5.58	5.53	5.93	6.36
F-10	4.90	5.60	5.86	5.60	5.68	5.87	
Serum Phosphatase (Milligrams Per Cubic Centimeter)							
B-2	14.35	14.14	12.48	12.05	11.29	10.45	12.07
A-3	15.36	13.48	14.30	11.86	11.59	10.96	12.25
D-6	11.78	13.51	11.40	10.64	10.13	11.31	9.54
E-8	18.00	15.01	13.39	11.86	11.43	9.54	14.76
F-10	16.93	15.42	14.51	12.05	11.47	10.47	

B-2 represents 200 Steenbock units. Number of patients treated—8.
A-3 represents 300 Steenbock units. Number of patients treated—11.
D-6 represents 600 Steenbock units. Number of patients treated—10.
E-8 represents 800 Steenbock units. Number of patients treated—10.
F-10 represents 1,000 Steenbock units. Number of patients treated—10.

Table III

Severe Rickets

Initials	Date	Age	Weight	Ca	P	P-tase	X-ray	Diet and Comments
M. S. (Colored) B. D.	1/29/35	16 mo.	17 lb. 8 oz.	9.41	3.15	52.73	A3+	G. +++, R. -+++, Ep. ++, H.S. +, Bowlegs +, No C.L.O. Br., C., V., W.M.
9/19/33	2/ 1			Medication started				800 St.U. per day
	2/ 5		18 lb.	9.09	3.70	58.34		
	2/11							Jeculin, teaspoonful t.i.d.
	2/12		18 lb. ½ oz.	9.04	3.59	36.01		Scraped beef
	2/18						B3	
	2/26		17 lb. 11 oz.	9.92	3.84	22.80	B3-	Cold W.M., C., V.
	3/ 4		17 lb. 10½ oz.					
	3/ 8		17 lb. 8½ oz.					Cervical adenitis, febrile
	3/12		17 lb. 1 oz.	10.64	3.68	18.83	B3	Cervical adenitis, V.P. (-) Chest x-ray neg.
	3/16		17 lb. 1 oz.					Blood transfusion
	3/26		18 lb. 1 oz.	11.40	4.83	15.41	B3	
	4/ 9		19 lb. 1 oz.	11.41	5.46	15.00		Eats well
	4/23		20 lb. 5 oz.	11.51	5.63	12.72	C	

G., Harrison's groove
R., rachitic rosary
Ep., widened epiphyses
H.S., head sweats
C.L.O., cod liver oil
Br., breast feeding
C., cereal
V., vegetable
W.M., whole cow's milk
St.U. Steenbock units
V.P., von Pirquet

had very severe rickets—serum phosphatase of 52.73 mg. which rose to 58.34 mg. per cubic centimeter. The phosphatase level fell under vitamin therapy and temporarily stayed at an elevated level—possibly the "plateau" effect of which Bodansky writes. The phosphatase content fell to normal, and the patient improved definitely only after blood transfusion. A blood transfusion was given because, even though he was under treatment, his hemoglobin fell from its initial level of 9.5 gm. to 7.5 gm. and his weight dropped from 18 pounds to 17 pounds, 1 ounce, in spite of efforts to bring it up. He had had slight cervical adenitis during this time, but his tuberculin reaction was negative, as was a chest roentgenogram and the Kahn test. After the blood transfusion his general condition promptly improved, his hemoglobin increased from 7.5 gm. to 11 gm., and his serum phosphorus and

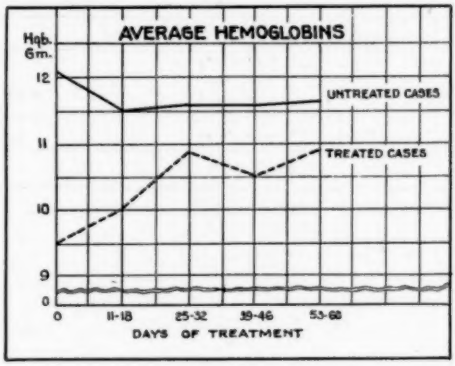

Chart 9.

phosphatase returned promptly to normal, although they had remained nearly stationary during more than a month of treatment of his rickets.

All told, there were 45 infants who had had blood counts and hemoglobin determinations. A chart of averages (Chart 9) shows that those receiving treatment with liver extract and iron,* though considerably lower (average initial hemoglobin, 9.5 gm.) than the untreated group (average initial hemoglobin, 12.2 gm.), made a definite gain of 1.3 gm. hemoglobin, while those receiving no iron and liver extract had finally an average hemoglobin 0.4 gm. lower than the average initial determination of 12.2 gm.

The rest of the blood picture, i.e., the red blood cell counts, white cell counts, and differential counts, showed the response expected in a secondary anemia. The experience at least demonstrates the necessity for taking into consideration the hemoglobin levels of the patients

*The commercial preparation, jeculin, was given in a dosage of three teaspoonfuls per day.

observed. The case (M. S.) cited may quite well have been considered a refractory one when, in reality, his failure to respond to vitamin D treatment was not due to lack of adequate vitamin D intake, but to his profound anemia and poor physical condition. On the basis of this experience, it is felt that since 71 per cent of the infants observed suffered from a secondary anemia, all patients with rickets should have some iron added to their medication unless examination shows their blood picture to be normal.

Average gains in weight per day for the various groups are shown in Table IV. All groups showed satisfactory gains.

TABLE IV

AVERAGE GAIN IN WEIGHT PER DAY

TREATMENT	GAIN IN OUNCES
Moderate and Severe Rickets	
B-2 (200 St.U. per day)	0.53
A-3 (300 St.U. per day)	0.49
D-6 (600 St.U. per day)	0.48
E-8 (800 St.U. per day)	0.41
F-10 (1000 St.U. per day)	0.54
Clinical Rickets With Mild Blood Changes	
B-2 (200 St.U. per day)	0.60
A-3 (300 St.U. per day)	0.61
D-6 (600 St.U. per day)	0.70
E-8 (800 St.U. per day)	0.60
F-10 (1000 St.U. per day)	0.57

In discussing the results of the observations, it seems proper to conclude that a basis for the more effective treatment of rickets with vitamin D as cod liver oil concentrate is offered. Dosages of from 600 to 1,000 Steenbock units per day are definitely superior to the smaller dosages. The optimal amount, as judged from this experiment, was 800 Steenbock units of vitamin D per day; from our experience, it seems safe to advise this dosage in the treatment of rachitic patients. According to the rate at which patients' serum phosphatase levels returned to normal, such high dosage should be continued for about forty-five to sixty days, after which time the dosage may be lowered, perhaps to the 300 Steenbock units per day level, since this latter figure seemed adequate to maintain the blood phosphorus level satisfactorily. Obviously, more severe cases need the longer periods of treatment.

We found that during healing the serum phosphatase did not maintain the plateau slightly above the normal as Bodansky reports, but rather that there was a gradual drop, the curve in all cases tending to follow the configuration of the die-away curve familiar to physicists.

With such wide variations as are commonly found between the clinical, roentgenologic, and older blood chemistry methods in the

diagnosis of rickets and with the difficulty observers have of agreeing on many of the points of x-ray diagnosis, the evidence submitted, we believe, supports the claim that serum phosphatase determinations are the most reliable, certainly in early or doubtful cases, in determining the rachitic state. Serum phosphatase determination offers us a mathematical standard which permits comparisons of various studies with the personal factor kept at a minimum; it offers aid in making earlier diagnoses and provides a more sensitive scale for evaluating the progress of the disease.

CONCLUSIONS

1. A total of 187 infants with clinical signs of active rickets and histories of low or no vitamin D intake was examined physically, roentgenologically, and by determining the serum calcium, the serum phosphorus, and the serum phosphatase during the winters of 1933-34 and 1934-35.

2. The agreement between serum phosphorus level and clinical findings (using a level of 4 mg. per cubic centimeter as indicative of active rickets) was only 19.8 per cent. If, however, the serum phosphatase levels between 6 mg. and 12.5 mg. per cubic centimeter are accepted as the normal range, then clinical and serum phosphatase agreement as to actual rickets is 65.2 per cent. Agreement between roentgenologic and clinical findings was only 26.7 per cent.

3. Data are submitted to support the establishment of the normal serum phosphatase for infants of this age group between 6 mg. and 12.5 mg. per cubic centimeter.

4. Serum phosphorus is demonstrated as unreliable as evidence of rachitic activity. Both the serum phosphorus determinations and x-ray examinations fail to show a large percentage of early actively rachitic infants.

5. Serum phosphatase determination appears to offer an excellent measure of rachitic activity and a means of determining rate and progress of healing.

6. The optimum dosage of vitamin D in the treatment of active rickets was 800 Steenbock units per day. This gave, in this experiment, significantly better results than a daily dosage of 600 or 1,000 Steenbock units per day. Treatment should include a minimum of 800 Steenbock units per day for a period of one and one-half to two months.

7. Secondary anemia is almost the rule with rachitic infants. If the anemia is severe, the patient appears to have a refractory case of rickets, when in reality the refractory quality is due to his poor general physical condition and disappears as his health improves. Treatment of the mild and moderate anemias with liver extract and iron

in addition to vitamin D led to improvement of the anemia with concomitant improvement of the rickets, and is felt to be an important item in the care of the patient.

We gratefully acknowledge the assistance of the Child Welfare Division of the Detroit Department of Health; the Out-Patient Department, laboratories, and X-ray Department of Harper Hospital, Detroit.

Funds and materials, including specially assayed vitamin D as cod liver oil concentrate, were furnished by the Upjohn Company, Kalamazoo, Mich.

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HUMAN BLOOD SERUM IN THE TREATMENT OF ANEMIA ASSOCIATED WITH JAUNDICE IN THE NEWBORN INFANT

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THE purpose in reporting three cases of anemia of the newborn infant treated with human blood serum is to reemphasize a simple procedure that is effective but which has apparently received little attention since it was advocated by Hampson for the treatment of icterus gravis.

In 1928 and 1929 Hampson[1] reported under the term "icterus gravis" a number of cases of severe familial icterus in newborn infants treated with human blood serum. This treatment was very successful. Eighteen babies were treated by this method, and seventeen recovered. In a collected series of ninety untreated cases, there were seventy-three deaths, a mortality of 81 per cent. His description of the findings in these patients deals largely with the bilirubin content of their blood in comparison with that of normal full-term infants. He gave serum daily in 10 c.c. amounts until the bilirubin content had fallen to one part in 150,000. The amount given was governed by daily estimations of the bilirubin content of the infant's serum. The average amount given was 30 c.c. His objection to the use of whole blood injections instead of serum was, first, the production of large hematomas which might easily become infected; second, the absorption of blood pigment which would increase the icterus in an already deeply jaundiced baby. His figures for the average amount of bilirubin in the normal full-term infant are one part of bilirubin to 75,000 parts serum. This is a somewhat higher figure for the normal full-term infant than the amount found by Mitchell[2] in studies on infants with physiologic jaundice (in the original article reported in terms of units). Mitchell's findings are tabulated in Table I, expressed in units, milligrams, and parts for comparison with Hampson's figures, and figures of the blood serum of two infants in this report.

If blood counts were taken, Hampson in his report did not give the figures. In light of the subsequent detailed and comprehensive reports of Diamond, Blackfan, and Baty[3] of similar cases of severe icterus in the newborn, accompanied by a marked increase in the erythroblasts, it would seem very likely that Hampson's cases were examples of erythroblastosis fetalis. However, Hampson states that the liver and spleen were not enlarged. In Diamond, Blackfan, and Baty's cases both liver and spleen were usually enlarged.

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Hampson's theory of the development of this type of jaundice is that normally there is a hormonic restraint in the mother's blood against hemolysis and that when this is withdrawn some infants who fail to elaborate this substance develop hemolysis of red blood cells and jaundice. According to this theory, the giving of human blood serum restores this restraining substance and stops hemolysis. Diamond, Blackfan, and Baty believe that in the erythroblastosis fetalis type of anemia the anemia may result from either a failure in the development and in the delivery to the circulation of normal erythrocytes or from rapid destruction of cells, or, most probably, from a combination of these factors.

TABLE I

BILIRUBIN CONTENT OF BLOOD SERUM OF NEWBORN INFANTS WITH PHYSIOLOGIC JAUNDICE

	UNITS	MG.	PARTS
		Mitchell	
Deeply jaundiced	20.2	1.81	1: 56,717
+++ jaundiced	10.6	0.83	1:123,646
++ jaundiced	8.7	0.436	1:235,589
+ jaundiced	7.8	0.39	1:260,461
		Hampson	
Normal full-term infant			1:75,000
		Infants in This Report	
Case 1 (Baby C.M., male)		9.61	1:10,671
Case 3 (Baby M., female)		9.15	1:11,218
		Adult normal 0.1-0.7	1:150,000 to 1:1,000,000

Blood serum of newborn infant, specific gravity 1.0265 or 102.65 gm. per 100 c.c.

The first infant in this report was treated in 1931 according to Hampson's method, as a case of icterus gravis. This was before erythroblastosis fetalis was described by Diamond, Blackfan, and Baty. The second patient, born June, 1934, was treated inadequately because of the fact that, in failing to find erythroblasts in the stained smear, I was convinced that it could not be a case of erythroblastosis fetalis, and therefore could not properly be treated by this method. The third case, though showing erythroblasts within the normal percentage range, was treated as a mild case of erythroblastosis fetalis.

The case records of the three infants were as follows.

CASE 1.—C. M., male, was born Jan. 4, 1931, a second child. Delivery was spontaneous, mother being in good health. No note was made of any discoloration of amniotic fluid. The infant acted normally after delivery and nursed well from the bottle and subsequently at the breast. No abnormality was noticed until January 7, when the infant was three days old. At this time the infant began to regurgitate, and he was moderately jaundiced. On the fourth day of life vomiting began; the baby became very listless; and the jaundice was very deep. The urine was dark in color. A marked pallor was perceptible so that the skin had a waxy yellow appearance. The infant seemed gravely ill. The spleen was just palpable, and, other

than this and the pallor and jaundice, physical findings were negative. The mother's blood serum (10 c.c.) was given intramuscularly. The infant was typed for transfusion. Within twenty-four hours the general condition of the infant was greatly improved, and the jaundice was visibly less marked. Transfusion was postponed, and for three subsequent days serum was administered, 12 c.c. the fifth day of life, 12 c.c. the sixth, totaling 34 c.c. of serum. By this time the jaundice had decreased, leaving the infant markedly pale. By the sixth day of life all signs of prostration had left. The infant was vigorous, nursed well from the bottle (it had been removed from the breast and the mother's breasts pumped in order to conserve the baby's energy). The van den Bergh test made on the fifth day showed a prompt negative reaction; indirect reaction 9.61 mg. per 100 c.c. of serum (specific gravity of serum of newborn infants, 102.65) or one part in 10,671 parts of serum. No more determinations were made since it was decided to give the average amount of serum found necessary by Hampson. It was felt that a fontanel puncture, removing 10 c.c. of blood daily for the van den Bergh reaction, was not advisable in a sick infant already anemic. The fragility test showed that hemolysis began at 0.42 per cent and was almost complete at 0.28 per cent. Mitchell[2] found in physiologic jaundice of newborn infants the same fragility of the red blood cells as in the nonjaundiced. He found that hemolysis began at 0.4 and was completed at 0.275 per cent. There was, therefore, no abnormal fragility. The infant was discharged on the fourteenth day of life, still pale but with no jaundice. The spleen was no longer palpable. A preparation of a secondary anemia liver fraction and iron and ammonium citrate (10 grain powder) was given twice daily in the formula. The response of the residual anemia was slow, and the infant was four months old before the blood count became normal. The blood counts of all three infants are in Table II.

CASE 2.—C. M., female, was born June 26, 1934. She weighed 5 pounds, 8 ounces at birth; she was the ninth child. Delivery was normal. Marked jaundice was noticed on the third day of life. She began to take her feedings poorly on the fourth day, with marked regurgitation. The child was lavaged and fed by gavage. I saw the infant on the seventh day of life and advised giving blood serum from the mother. After 15 c.c. of blood serum was given intramuscularly, a blood count was made. This showed 2,630,000 erythrocytes, 18,200 leucocytes, 11.2 gm. of hemoglobin (66 per cent, Newcomber). No nucleated red blood cells were seen, and the red blood cells appeared normal. There was considerable improvement in the general condition. Regurgitation was less marked, and in a few days' time there was a notable improvement in the jaundice. As I was of the opinion at that time that probably only an erythroblastic type of anemia would respond to serum, I advised no more. Lextron, a liver and stomach extract, with iron ammonium citrate, one capsule a day, was given.

By the thirteenth day of life all jaundice was cleared, and the severe anemia was evident. The baby was discharged on the nineteenth day, weighing 5 pounds 10 ounces, 2 ounces over birth weight. She was not regurgitating but was not taking her feedings well; at the time of discharge she was receiving an artificial formula because it was impossible to obtain milk from the mother with the electric breast pump. The child was brought to Northwestern University Medical School Dispensary the next day, where the first count showed 1,630,000 erythrocytes and 5.8 gm. of hemoglobin (39 per cent Sahli). The lextron capsules were increased to two a day, totaling 15 grains, 1 gm. liver and stomach extract, and 6 grains of iron ammonium citrate. She was brought back the following week. The infant had gained 4 ounces in weight during the week, but she was still taking her feedings with difficulty. The blood count showed little improvement: erythrocytes, 1,880,000; hemoglobin, 5.6

TABLE II

DATE	R.B.C.	HEMOGLOBIN			W.B.C.	N.	E.	B.	LY.	MONO.	RETICULOCYTES (%)	SPECIAL FEATURES
		GM.	%	METHOD								
Case 1. Baby C. M., Male												
1/ 9/31 5th day of life	2,700,000		55	Newcomber	16,800						5.2	Poikilocytosis, anisocytosis, no erythroblasts.
1/14/31	2,890,000		56	Newcomber	10,800	69			30	1	1.8	Poikilocytosis, anisocytosis still present.
2/16/31	3,700,000		60									
3/30/31	3,850,000		58									
5/ 6/31	4,000,000		75									
Case 2. C. M., Female												
Wesley Memorial Hospital												
7/ 3/34	2,630,000	11.2	66	Newcomber	18,200							No nucleated reds. Red blood cells appear normal.
Northwestern University Medical School												
7/13/34	1,630,000	5.8	39	Sahli	7,100	39	1.5		54	5.5		Poikilocytosis very slight; antisocytosis slight. Basophilia moderate. Polychromatophilia many cells.
7/20/34	1,880,000	5.6	37	Sahli								
7/27/34	3,050,000		55	Sahli								
8/20/34	3,430,000	9.0	60	Sahli								
9/11/34	3,660,000	9.2	61	Sahli								
9/26/34	3,440,000	9.8	65	Sahli								
10/26/34	4,980,000	11.4	76	Sahli								
11/ 2/34	5,060,000	14.0	92	Sahli								
Lextron discontinued												
2/ 4/35	4,830,000											
3/29/35	5,140,000											
5/ 8/35	4,660,000	11.0	76	Sahli								

TABLE II—CONT'D

DATE	R.B.C.	HEMOGLOBIN			W.B.C.	N.	E.	B.	LY.	MONO.	RETICULOCYTES (%)	SPECIAL FEATURES
		GM.	%	METHOD								
Case 3. Baby M., Female												
2/ 6/36 4th day of life	4,740,000	15.2	90	Newcomber	24,400	72	4	1	19	4		7 erythroblasts.
2/ 8/36	3,590,000	13.5	80	Newcomber	10,850	65	1		29	5	0.8	No erythroblasts. Marked anisocytosis.
2/10/36	3,030,000	10.8	74	Newcomber	9,500	66	4		28	2	2.4	No erythroblasts.
2/11/36	2,960,000	12.0	71	Newcomber	10,900	70			29	1	1.6	
2/12/36	2,720,000	10.8	64	Newcomber							1.6	
2/13/36	2,770,000	9.8	58	Newcomber							1.0	
2/14/36	2,880,000	10.35	61	Newcomber							0.8	
2/16/36	2,840,000	10.0	60	Newcomber							0.8	
2/17/36	2,615,000	10.3	61	Newcomber							2.3	
Counts at Cradle Nursery												
3/ 2/36	4,560,000	9.48	60	Tallqvist	8,650	49	1	1	30	19		
3/ 3/36	4,300,000	12.07	56	Sahli	7,950							
3/ 5/36	4,010,000	12.41	53	Sahli	8,000	34	2	1	55	8		Many platelets and marked red cell destruction.
3/ 8/36	3,900,000	12.41	53	Sahli	7,700	12	0	0	56	32		
3/ 9/36	3,790,000				7,350	17	2	1	72	10		
3/10/36	3,520,000	11.0	65	Sahli	5,500	19	2	0	79	0		R.B.C. practically normal.
3/13/36	2,920,000	11.0	65	Sahli	5,500	33	0	0	65	2		
First pertussis vaccine												
3/19/36	2,920,000	10.2	60	Sahli	5,100	33	0	0	65	2		
3/20/36	¾ grain iron citrate, hypodermically. Dicalcium phosphate and iron by mouth.											
3/23/36	3,120,000	10.2	60	Sahli	9,950	45	0	0	40	15		
3/29/36	4,050,000	11.0	65	Sahli	4,100	18	0	0	72	10		
4/ 5/36	3,560,000	11.0	65	Sahli	6,000	30	0	0	68	2		

gm. (37 per cent Sahli). On the following weekly visit the infant showed a marked improvement, having gained 6 ounces in weight, and did not look anemic. The blood count showed 3,050,000 erythrocytes and 55 per cent hemoglobin (Sahli). There was little change in the count on subsequent visits until Oct. 26, 1934, when the infant was a little less than four months old. The count then showed 4,980,000 erythrocytes and 11.4 gm. hemoglobin (76 per cent Sahli). Lextron was discontinued. Subsequent counts taken until the eleventh month of life showed no recurrence of the anemia. The child's development has been good to the present time.

CASE 3.—Baby M., female, was born Feb. 3, 1936, by cesarian section. Her condition was good after delivery. The infant took fluids well, regurgitating small amounts during the first twenty-four hours. Regurgitation became more marked on the second day and by the third day was very severe. By the fourth day the infant was gravely ill. Respirations were rapid, and, when she was seen on the evening of the fourth day, oxygen had to be administered almost continuously. At one time during the examination respirations ceased and artificial respirations had to be instituted. The color of the skin was a deep yellow; the sclera were deeply jaundiced. General physical examination revealed nothing to account for the condition. The spleen was not palpable and no abnormalities were found. Because of the jaundice with normal bile colored stools and a dark bile colored urine, a tentative diagnosis of congenital anemia of erythroblastic type was made. Adrenalin was administered as a stimulant, and the oxygen and carbon dioxide mixture was continued. Subcutaneous glucose was given. The first blood count, taken that evening, showed only a moderate fall in red blood cells and hemoglobin; erythrocytes, 4,700,000; hemoglobin, 90 per cent. There were 24,400 leucocytes; 7 per cent erythroblasts, or 1,708 of the total white blood cells. This was high but within the normal figures of 2 to 30 per cent of erythroblasts in the cell count of newborn infants. However, 10 c.c. of human blood serum was administered intramuscularly. The next day the infant's general condition was very much improved. There was a continued drop in the blood count, to 3,590,000 erythrocytes and 80 per cent hemoglobin, with no erythroblasts seen. Vomiting continued even with gavage, and a No. 8 catheter was allowed to work its way into the duodenum like a Levine tube. After eight feedings were given by this method, food was retained in 1 ounce amounts given every two hours by bottle. Supportive subcutaneous fluids were continued. Another 10 c.c. of human serum was administered on this and on two succeeding days, totaling 40 c.c. in all. There was a marked steady improvement each day in the general condition, though there was a continued fall in the red blood cell count and hemoglobin content until the tenth day, when they remained about stationary.

The van den Bergh test made on the seventh day of life showed direct delayed one-plus reaction; indirect, 9.15 mg. per cent per 100 c.c. serum, approximately one part in 11,218 of serum. The sclerae were still jaundiced; the skin was slightly jaundiced. The red blood cell fragility test taken on the tenth day of life showed that hemolysis began at 0.46 per cent and was not quite complete at 0.28 per cent. All clinical signs of jaundice had disappeared by the tenth day. A liver and stomach extract with iron, lextron, two capsules a day, were given from the ninth to the fourteenth day. The baby was discharged to the Cradle Nursery when fourteen days old, weighing 6 pounds 3 ounces; the birth weight was 6 pounds 5 ounces. The blood counts after discharge were taken through the courtesy of Dr. Louis Sauer, to whom I am indebted also for a complete report of the medication used and the progress made by the infant.

Upon entering the Cradle on Feb. 17, 1936, the fourteenth day of life, the infant received no medication until March 20, when she was forty-five days old. During this

time there was a steady fall in the red blood cell count, from a count on March 5 of 4,010,000 to 2,292,000 on March 19. At this time iron citrate was given by deep hypodermic injection every other day, and 1 dram of the mixture:

Ferric pyrophosphate	40	
Alcohol 95 per cent	52	5
Copper sulphate	1	6
Aqua dest. q.s.	1,000	

This medication produced definite improvement in fiifteen days, from 2,920,000 erythrocytes to 3,560,000.

I was given an opportunity to examine the infant at this time, and she was to all appearances not anemic. The physical findings were negative, and the state of nutrition was excellent.

Whether or not these three infants had the blood dyscrasia known as erythroblastosis fetalis is difficult to state. In two no erythroblasts were noted by the pathologist who examined the stained smears. In the third case 7 per cent, or 1,708, erythroblasts were found, on the basis of the leucocyte count of 24,400—a high count, but well within the normal range of 2 to 30 per cent found in the newborn infant. All three infants were deeply jaundiced. In the two whose serum was examined, a high bilirubin content was present. Since one was a second child, one a ninth, and one a first child, a familial history is absent. Only one had an enlargement of the spleen, usually present. In none did the obstetric notes report yellow colored amniotic fluid.

Cohen[4] has reported a case of severe anemia without jaundice and without erythroblastosis and a case of severe jaundice with erythroblastosis without anemia, and he concludes that anemia of the newborn and erythroblastosis are not synonymous. There are apparently two different types, one in which there is a failure of regeneration, in the other an increased hemolysis plus a failure in regeneration. Milder forms of both probably occur. It becomes apparent when reviewing the literature that the deeply jaundiced type, those with a probable increased hemolysis, are the more severe. In Abt's collected series[5] there were seven who received no treatment. Two of the early deeply jaundiced patients died. In the five who recovered without treatment, three had slight jaundice, one from the first to the fifth day, one on the second and third days, and one from the first to the sixteenth day. The remaining two had no jaundice, showing that symptoms are milder without jaundice. The prostration of these infants in my report, Cases 1 and 3, was greater than one would expect from the anemia present. In reading the histories of reported cases of erythroblastosis fetalis and congenital anemias of the newborn, one is struck by the frequency of the prostration described. In all three cases the first injection of serum made a marked improvement in the general condition. This almost toxic state may be due to the excessive amounts of blood pigments in the circulating blood plus the anemia. Hampson[1] reports

that in the adult rabbit the products of the destruction of red cells are not toxic when injected, but that in the pregnant animal death of the fetus and abortion occur. The growth of young animals receiving injections of the hemolysed blood cells was retarded. Normal adult serum apparently restores a deficient substance which regulates and retards blood destruction.

The excessive jaundice in these three patients and others reported of the same type is probably explainable on the basis of increased blood destruction. Goldbloom and Gottlieb[6] explain physiologic jaundice on the basis of a difference in oxygen tension. Their explanation of physiologic jaundice is that it is simply an excess over the normal mechanism of cell destruction which occurs after birth. They find an increased fragility of red corpuscles of cord blood, which returns to normal in about one week. Immature forms are more sensitive to saline dilution. Reticulocytes disappear first, nucleated red cells second. Before birth the infant's cells are in a state of anoxemia and the difference in oxygen tension causes the increased fragility. This is contrary to the findings of Mitchell[2] and Hampson.[1] In Case 1 hemolysis began at 0.42 per cent and was almost complete at 0.28 per cent, and in Case 2 hemolysis began at 0.46 per cent and was almost complete at 0.28 per cent. In severe cases the infants are born jaundiced. No difference in oxygen tension should exist in utero between one pregnancy and another unless the placenta was defective, and this has not been reported.

Mention should be made of Huenekens' recent report[7] of a case of anemia of the newborn without jaundice, treated with a stomach and liver extract and iron (lextron). Both in his patient and the one reported by Schwartz[8] marked improvement resulted when large doses of this substance were given. He offers for further study the theory that these anemias of the newborn are due to a deficiency in the same liver and stomach substance or fraction described by Castle,[9] the continuous giving of which keeps the blood of pernicious anemia patients up to normal limits. In Case 1 a secondary anemia fraction of whole liver and iron was given, without spectacular results but with continuous improvement.

In Case 2 a probably inadequate amount of liver and stomach extract and iron was given, with little improvement until two capsules of 15 grains daily were given, when the count went up from 1,880,000 red blood cells to 3,050,000 in one week.

In Case 3 the liver and stomach extract was given for only five days, from the ninth to the fourteenth day. A count taken when the infant was twenty-six days old was 4,740,000, hemoglobin 53 per cent. Then there was a lapse of all medication until the child was forty-two days

old, when the blood count was 2,292,000. Iron injections and iron medication by mouth were then started, with a gradual improvement in the blood picture.

Though both Huenekens' patient and that of Schwartz were without jaundice and my three patients were jaundiced, there is apparently a failure in regeneration in the jaundiced cases as well. The response in Case 2 was so prompt on increasing the liver and stomach extract and iron preparation that this theory has considerable appeal.

SUMMARY AND CONCLUSIONS

Three cases of anemia of the newborn associated with severe jaundice are reported. They were probably of a mild erythroblastosis type. They were treated by daily injection of 10 c.c. to 12 c.c. of blood serum for one, three, and four days, respectively. Marked improvement in the general condition immediately followed. The method is not suggested to supplant transfusion which restores blood as well as a probable deficient substance restraining hemolysis. It is simple and can be carried out by anyone possessing a centrifuge with tubes and a large syringe. As it seems effective, it should have its place in the treatment of the icteric type of anemia of the newborn infant.

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CONGENITAL OBSTRUCTION OF THE ALIMENTARY TRACT

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EIGHT cases of congenital obstruction are reported. In order of their frequency obstruction is found most commonly in the ileum, duodenum, colon, and esophagus. The first recorded case of intestinal obstruction was reported by Osiander[1] in 1797. The next reported case was in 1808 by Aubrey.[2] Theremin[3] in 1877 was the first to review the literature and make an exhaustive study of congenital intestinal obstruction. He found that out of 150,000 children cared for at a foundling institution in Petrograd there were nine cases of intestinal obstruction and two cases out of 110,000 children in a similar institution in Vienna, making the frequency from 1 to 16,000 to 1 to 55,000, respectively.

The earliest reported congenital malformation of the esophagus was described by Durston[4] in 1670. Thomas[5] quotes a description of esophageal atresia from Gibson's *Anatomy*, a popular book in the seventeenth century (November, 1696). Schoeller[6] in 1838 reported a case of esophageal atresia with tracheal communication, and stated that the only previously reported cases of that type were in 1825.

CASE 1.—S. T., No. 31059, a male infant, five days old, was admitted to the babies' wards, Jamaica Hospital, Jan. 30, 1928, and died Feb. 1, 1928.

Delivery was normal. There was a history that the infant was moderately cyanotic and that he had aspirated a good deal of mucus; he was breast fed but was unable to retain feeding. Vomiting was not projectile but a few minutes after feeding there would be an oozing of milk from the mouth. On admission the temperature was 102° F. The infant's weight was 5 pounds 15 ounces.

He was dehydrated and had a very weak cry. The infant did not respond to atropine therapy, continued to vomit, regurgitated food through his mouth and nose. A catheter was passed and an obstruction was encountered about midway down the esophagus. The regurgitated food examined did not contain hydrochloric acid. There were no other abnormalities present. Attempts to visualize the stomach by means of barium feeding were unsuccessful, because of the apparent esophageal obstruction. A surgical consultation was obtained. Gastrostomy was considered, but it was deemed inadvisable because of the condition of the infant. The infant died Feb. 1, 1928, forty-eight hours after admission.

Autopsy Report.—The esophagus started from the pharynx as a tube 0.75 cm. in diameter, of fairly thick walls, which ended blindly after 3 cm. at the tracheal bifurcation, thus forming a closed pouch. Slightly above this blind pouch there was a small fistulous tract running upward and communicating with the trachea. A second esophagus started from the pharynx as a flat muscle layer forming part of

From the Department of Pediatrics of the New York Post-Graduate Medical School and Hospital of Columbia University, and of Jamaica Hospital. The author is indebted to Dr. E. E. Brown for the diagrammatic drawings.

the posterior wall of the trachea and facing the lumen of the latter. Slightly above the level of the bifurcation of the trachea (5 mm.) this wall closed to a slit which represented the opening of the esophageal tube which, after a straight course of 6.5 cm. and 0.4 cm. at the widest diameter, ended in the stomach which showed normal configuration. The latter part of the esophagus admitted a narrow probe throughout.

Lungs.—The lungs showed patches of consolidation and congestion in all lobes, both sides, mostly within the lower lobes. The heart showed no abnormalities. The intestines and all other organs showed no abnormalities except those due to severe dehydration.

Diagnosis.—Congenital atresia of the esophagus with esophagotracheal fistula of the upper segment; aspiration pneumonia; and inanition.

The following very recent case seen at the Queens General Hospital is the more common and classic type of esophageal atresia.

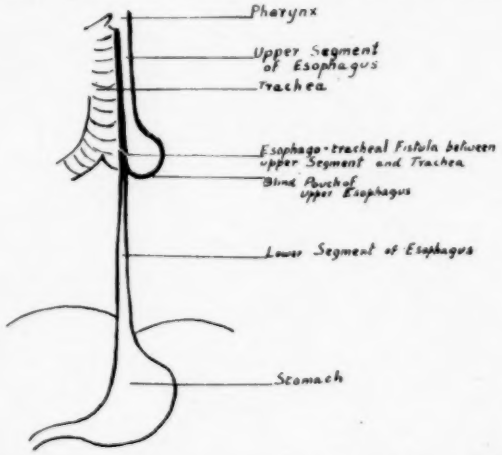

Fig. 1.—Congenital atresia of esophagus (Case 1) with esophagotracheal fistula between upper segment and trachea (diagrammatic).

CASE 2.—A. L. S., No. 25969, a male infant, white, was born at the Queens General Hospital Sept. 2, 1936, and died Sept. 21, 1936.

The baby's birth weight was 6 pounds 12 ounces. Since birth there had been an almost continuous oozing of mucus from the mouth. The throat was full of mucus, and there was some cyanosis particularly during feeding. The infant took very little of the formula, and there was regurgitation of food through the mouth and nose. A diagnosis of esophageal atresia was made; the atresia was confirmed by x-ray. An emergency consultation was held, and it was decided to do a gastrostomy. The postoperative course was complicated by continuous oozing of blood from the wound, which necessitated a transfusion. The infant was fed through the gastrostomy wound, did well for a time, and gained weight. On September 17, the infant began to regurgitate, through the mouth, material that had all the characteristics of partly digested milk, which is strong evidence in favor of a communication between the lower segment and the trachea or bronchus. Preparations were made to trace this tract with barium feeding through the gastrostomy wound, but un-

fortunately the infant developed aspiration pneumonia and died before this procedure could be carried out. Autopsy could not be obtained.

Diagnosis.—Esophageal atresia with probable communication between the lower segment and trachea, and aspiration pneumonia.

Esophageal atresia is extremely rare. Cautley[7] in twenty-five years of hospital practice saw only one case. Shukowsky and Baron[8] reported one case in 50,000 new births. In spite of this rarity Brennemann[9, 10] reported three cases of congenital esophageal atresia in

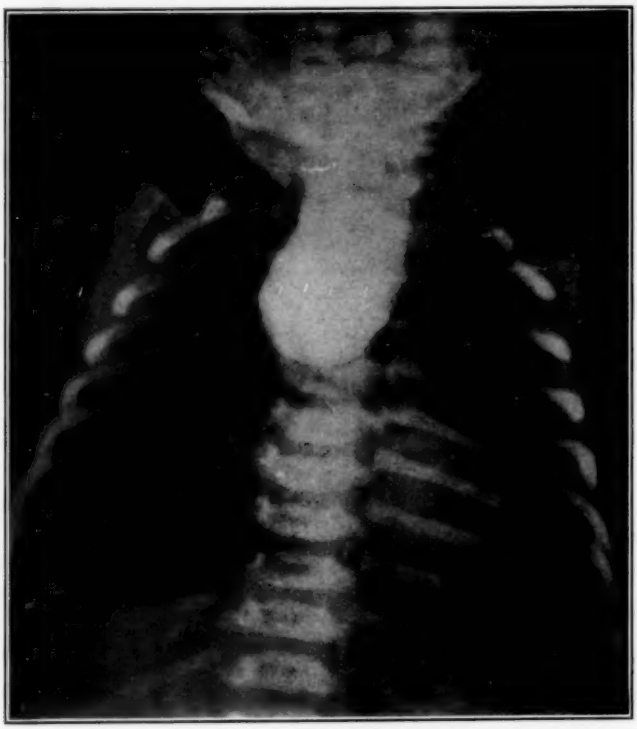

Fig. 2.—A. L. S. (Case 2), esophageal atresia.

1913 and four more in 1918. Hirsch[11] was able to find only 146 verified cases reported in the literature. Several types of atresia have been reported; the most common is that in which the lower segment communicates with the trachea at about the level of the bifurcation or occasionally with a bronchus as was probable in Case 2. Communication between the upper segment and trachea as in Case 1 is a comparatively rare type although in still rarer instances both upper and lower segments may communicate with the trachea. The characteristic symptoms are immediate regurgitation with almost the first

mouthful, depending on the height of the obstruction. The upper respiratory tract is full of mucus with almost constant dribbling, and the vomitus is a combination of mucus and milk. In a third case seen in consultation several years ago, the infant had the characteristic symptoms of esophageal atresia with tracheal or bronchial communication. Immediately after feeding the infant became cyanotic, coughed

Fig. 3.—Classic case of congenital atresia of the esophagus. Probe (black) shows communication between the lower segment of the esophagus and the trachea at the bifurcation. Upper segment ends in a blind pouch and is partly hidden by the thyroid (Brennemann[9,10]).

violently, had numerous râles in the chest, and vomited. The stools of these infants are made up entirely of meconium. Loss of weight is rapid; the infant may live from a few days to one or two weeks. Most of these infants succumb either to inanition or to aspiration pneumonia. All types of atresia are possible, from a complete absence

where the cardiac end of the esophagus is connected with the mouth end by a fibrous cord, to a partial atresia with only a narrowing of the lumen. There may even be tracheobronchial communication without atresia (Cautley[7]). Partial atresia, when it does occur, may not always be recognized soon after birth as is evidenced by the following case.

CASE 3.—M. C., No. 84167, a male child, two years and three months old, was admitted to the babies' wards, New York Post-Graduate Hospital, March 24, 1931.

There had been vomiting since the child was two weeks of age. The vomiting was questionably projectile. The intervals in which the child was free from vomiting varied from a few days to two months. For the past six or seven months there had been vomiting about every two to four weeks for periods of two to three days. He had been on atropine therapy since early infancy. About twelve days previous the vomiting had increased in frequency and intensity. It occurred after every feeding and between feedings. Vomitus has never been tinged with blood. On further questioning an additional history was elicited. Two weeks previous the child had swallowed a cherry pit, causing considerable choking. His mother was unable to make him vomit the pit.

X-ray films with barium revealed a marked esophageal obstruction about two inches above the diaphragm, with marked dilatation of the upper two-thirds of the esophagus with a narrow canalization continuous below the point of the obstruction, permitting some of the contrast medium to enter the stomach, with the conclusion that there is a partial obstruction of the lower third of the esophagus.

Esophagoscopy revealed the stricture about eight and one-half inches from the incisor teeth with enormous dilatation above. The cherry pit was found at the point of stricture and removed. A reexamination of the esophagus with barium, after the removal of the foreign body, showed a diminution of the obstruction which resulted from the removal of the pit but showed a contraction with canalization in the lower third of the esophagus. The patient was repeatedly admitted for dilation with bougies; he did well, gained weight, and was able to eat solids. Ulceration developed at the area of the stricture, and it was necessary to perform a gastroenterostomy and retrograde dilation was performed later. The child subsequently developed pneumonia, bilateral empyema, and a positive blood culture due to the hemolytic streptococcus. He died May 22, 1933.

Autopsy Report.—A stricture of the esophagus was found at a level of the aorta extending to the cardiac orifice, and there was complete mucosal ulceration of the esophageal area of the stricture and with muscular hypertrophy.

In the absence of any cause for the abnormally narrow lumen of the lower third of the esophagus one may be justified in concluding that the above case is one of partial congenital esophageal stenosis that was brought to light by the swallowing of the pit, particularly in view of the history of persistent vomiting soon after birth.

In 1901 Cordes[12] collected 56 cases of congenital obstruction of the duodenum and reported one of her own. She made a study of the clinical and pathologic findings and stated that occlusions of the small intestines occur most often in the duodenum. However, according to the classification of congenital intestinal obstruction as to sites, from 328 cases which Spriggs[13] collected from the literature, the ileum is the most frequent location.

CLASSIFICATION OF THE POSITION OF THE CONGENITAL INTESTINAL OBSTRUCTION IN 328 CASES

Duodenum	92 cases	28 per cent
Above papilla	29 cases	
Opposite papilla	17 cases	
Below papilla	21 cases	
Duodenojejunal junction	15 cases	
Unclassified	10 cases	
Jejunoileum	124 cases	38 per cent
Unclassified	55 cases	
Lower ileum and in the immediate vicinity of the ileocecal valve	69 cases	
Colon	20 cases	6 per cent
Unclassified	28 cases	8 per cent
Multiple occlusions	64 cases	20 per cent

CASE 4.—M. B., No. 61648, a male infant, one month old, was admitted to the babies' wards, New York Post-Graduate Hospital, Jan. 3, 1931, and died Jan. 31, 1931.

The infant vomited several times during the first forty-eight hours. For an interval of about three weeks the infant was apparently well, then he began to have projectile vomiting immediately after each feeding. He was given a thorough trial

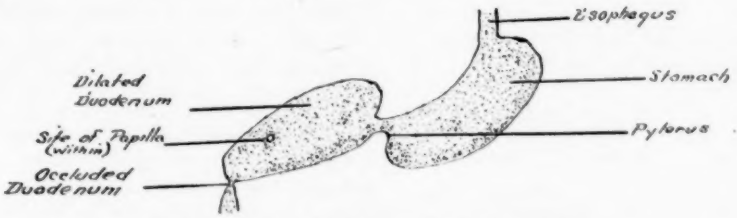

Fig. 4.—Case 4. Congenital occlusion of duodenum.

with atropine but with no success. While he was in the hospital, it was noticed that the vomitus sometimes contained bile. X-ray examination showed duodenal dilatation. A diagnosis of partial intestinal obstruction (duodenojejunal) was made because of dilatation of duodenum. A gastroenterostomy was performed. The infant did very well for about a week, then a fecal fistula developed. He was operated on for the repair of the fistula. He died within forty-eight hours after repair.

Autopsy Report.—There was a generalized peritonitis; and a congenital partial obstruction at the distal end of the duodenum.

In twenty of the cases Cordes[12] collected, the duodenal obstruction was above the level of the papilla, in thirteen it was below the orifice, and in two it was on a level with the duct. The symptoms are those of intestinal obstruction with either the stools or the vomitus containing bile, depending on the location of the occlusion to the papilla and whether the obstruction is partial or complete. The differential diagnosis between congenital duodenal obstruction, particularly when it is above the opening of the bile duct, and pyloric stenosis is obviously difficult. An x-ray film with barium feeding will be of considerable help.

The following is an interesting case of congenital obstruction of the ileum with successful results:

CASE 5.—R. B., No. 57979, a male infant, four days old, was admitted to the babies' wards, New York Post-Graduate Hospital, Aug. 12, 1930, and was discharged Sept. 6, 1930.

The infant, breast fed, had had no bowel movement since birth. On the day of admission he started to vomit fecal material, which vomiting continued all day. Barium colon enema showed an intestinal obstruction probably at the right ileocolonic area. On operation the intestinal obstruction was confirmed. Atresia was apparently complete somewhere in the midportion of the ileum. The gut was continuous but the canal was not. The ileum was so small that it was necessary to use sigmoid for sigmoidostomy. The patient was discharged in good condition. Attempts to find out whether the patient was still alive to date were futile because of frequent changes in address.

The most common type of congenital intestinal obstruction is the complete type. The gut may end in a blind pouch, the ends may be connected by a fibrous cord, or the gut may be continuous with no canal as in the above case. However, partial atresia of the intestines does occur, similar to the case of partial esophageal atresia quoted above (Case 3, M. C.). The following two cases at Jamaica Hospital illustrate the two types of atresia, partial and complete. Both involved the colon.

CASE 6.—D. T. W., No. 68114, a male infant, was born Sept. 7, 1935, at Jamaica Hospital and died Nov. 13, 1935. His birth weight was 4 pounds and 8 ounces.

He was a seven-month premature infant delivered by cesarean section. The baby was born in apparently good condition of an eclamptic mother, and had a strong cry. He vomited for the first twenty-four hours and irregularly thereafter. I was called in consultation on October 4 because the baby's head was getting larger. The infant was malnourished, dehydrated, weighed 4 pounds 7 ounces, and had a hydrocephalic type of head. All sutures were widely separated, the posterior fontanel was open. In the next few days the baby vomited profusely, projectilely, which was controlled by atropine sulphate gr. $\frac{1}{500}$. On October 9, he developed an unaccountable temperature of 105° F. which persisted for two days. Atropine was discontinued and vomiting was controlled by luminal. The infant improved considerably and gained weight, and his head did not increase greatly in size. The stools were pasty and well digested. On November 5, he began to develop abdominal distention which at first responded to castor oil but later became persistent. The stools were pasty, and the nurses were unable to give a satisfactory enema because the tube became clogged in a mass of soft pasty feces. Abdominal distention progressed, and I was able to outline the colon on the right side of the abdominal wall and thought at first that I was dealing with a congenital megacolon. A flat plate and barium enema were ordered.

X-ray Findings.—Fluoroscopy: The baby was unable to hold more than 50 c.c. of barium which reached the splenic flexure. The colon thus outlined did not appear unusually dilated. The barium was not retained.

Flat plate: There was a great deal of gaseous distention which appeared to be in the small intestine, giving almost a ladder appearance. The impression of the roentgenologist was that there appeared to be an obstructive condition in the small intestine.

In the meantime the head increased in size, the vomiting recurred, and the distention grew progressively worse. The infant died Nov. 13, 1935.

Autopsy Report.—There was a comparatively large head, with the skull enlarged posteriorly. Fontanels were markedly enlarged and sutures separated. The brain was soft and boggy with enlarged lateral ventricles. The kidney showed fetal lobulation. The large intestines revealed a partial atresia with narrow canalization from the splenic flexure down (about one-third the normal size) with marked dilatation above that point. The lungs showed consolidation and congestion of both pulmonary bases.

CASE 7.—Baby M., No. 71057, a female infant, was born April 21, 1936, weighing 7 pounds and 8 ounces, was admitted to Jamaica Hospital when thirty-six hours old.

She had vomited since birth. Vomitus was sometimes bile stained. According to the nurse the baby had had one meconium stool the day before admission, none since. In the hospital the stools consisted of mucus. She was given an enema; nothing but mucus was obtained. The abdomen was distended and tense. Rectal examination revealed much mucus with a little blood on the examining finger. In view of the bile-stained vomitus, abdominal distention, and rectal findings, I made a diagnosis of either intussusception or congenital intestinal atresia. The infant was operated on within the hour.

Operative Findings.—A large amount of free serous fluid was present in the peritoneal cavity. The large intestine was cordlike in appearance, had no lumen, and began at a point near the rectum and extended to the hepatic flexure. Beyond this point the intestines were markedly distended. Ileostomy was performed. There was a large amount of impacted meconium in the intestines. The baby was in shock following the operation. Her temperature rose to 104° F. Meconium was passed from the abdominal wound and her condition became rapidly worse. Peritonitis developed, and the baby expired at 9:15 A.M. on April 25, 1936.

Congenital intestinal occlusions are generally single and occur most often in the lower ileum. Multiple occlusions occur most often near the jejunoileum junction. They may be associated with other malformations, such as spina bifida and imperforate anus, or as in Case 6 in which there was hydrocephalus. The symptoms are those of obstruction with vomiting, distention, constipation, and anuria. There may be some meconium passed. The frequency of the vomiting and the amount of distention are dependent on how far down the intestinal tract the obstruction is located. The farther down the obstruction is, the greater the distention, the less frequent the vomiting, and the fewer are the meconium stools. Other conditions that may produce congenital obstruction are fetal accidents such as volvulus and kinks and congenital peritonitis, either tuberculous or syphilitic in origin. Although fetal peritonitis is extremely rare, Cordes[12] mentions three cases in which the obstruction was due to fetal peritonitis and quotes the case of a full-term child with intestinal obstruction due to tuberculous peritonitis, who lived six days. The following case is an unusual type of intestinal obstruction in a newborn infant which exemplifies the group classified as fetal accidents.

CASE 8.—J. R. R., No. 54513, a male infant, two days old, was admitted to the babies' wards, New York Post-Graduate Hospital, April 15, 1930, and died April 16, 1930.

There had been no bowel movement and no flatus since birth. There was bloody return to an enema. The vomitus was bile stained. The abdomen was markedly distended and rectal examination revealed blood on the examining finger. An exploratory operation failed to locate the obstruction; however the lower ileum was found tightly contracted. The baby died twelve hours later.

Autopsy Report.—There was gangrene of the jejunum and mesentery due to volvulus. Localized peritonitis was present, and patent ductus arteriosus, cardiac hypertrophy and dilatation, and bronchopneumonia were also revealed.

Whether the volvulus occurred before or after birth, it is difficult to say. The symptoms appeared immediately after birth and it may be that the volvulus occurred before birth.

A very practical and simple procedure for differentiating between a complete obstruction and an incomplete intestinal obstruction or none at all is the examination of the meconium. Meconium is passed even in a complete obstruction, particularly if it is a high one, although it is interesting that in Case 7 with complete obstruction of the colon

Fig. 5.—Types of congenital obstruction reported.
I, The gut ends in a blind pouch as in Cases 1 and 2.
II, Partial atresia with narrowing of lumen as in Cases 3 and 6.
III, Partial atresia at one point as in Case 4.
IV, Complete atresia with the gut continuous but the lumen not continuous as in Cases 5 and 7.

from the hepatic flexure down to a point near the rectum, the nurse reported one meconium stool. The composition of meconium includes vernix caseosa, epithelial cells, and lanugo hairs swallowed with the amniotic fluid. Meconium stools may persist for as long as four days, after which they are followed by the milk feces. In the newborn infant with profuse vomiting in whom intestinal obstruction is suspected, the presence of either hair or vernix caseosa would indicate that there is no gastrointestinal obstruction, or, if there is one, it is partial or incomplete. The vernix caseosa has a distinct microscopic appearance in that sheets of cornified epithelial cells are found which are characteristic and cannot be mistaken for anything else.

A modified classification of congenital obstruction of the gastrointestinal tract is proposed from an etiologic standpoint.

1. True congenital obstruction developmental in origin, as in Cases 1, 3, 4, 5, 6, and 7.

2. Congenital obstruction with acquired characteristics.
   a. Fetal accidents such as volvulus intussusception and kinks as in Case 8.
   b. Fetal peritonitis.

SUMMARY

Eight cases of congenital obstruction of the alimentary tract are reported.

1. Congenital esophageal atresia with communication between the upper segment of the esophagus and the trachea.
2. Congenital esophageal atresia with probable communication between the lower segment and the trachea.
3. Partial atresia of the esophagus with narrowing of the lower one-third. The characteristic symptoms of atresia of the esophagus are immediate regurgitation with almost the first mouthful, and constant dribbling of mucus. There may or may not be violent coughing after feeding, with cyanosis.
4. Case of partial atresia of distal end of duodenum. Duodenal obstruction is to be differentiated from pyloric stenosis. The presence of bile in the vomitus, and x-ray examination with barium feeding will aid in the diagnosis.
5. A successful operative result of congenital obstruction of the ileum.
6, 7. Incomplete and complete obstruction, respectively, of the colon.
8. Obstruction due to volvulus with symptoms immediately after birth.

It is interesting to note that of the eight cases reported seven were males. The symptoms of congenital intestinal obstruction are characterized clinically by persistent vomiting, distention, constipation or mucous stools stained with blood, anuria, and progressive loss of weight. Although congenital obstruction is very rare, it should be kept in mind whenever a newborn baby vomits. It is obviously important to recognize these cases early because operative intervention is the only treatment, however unsuccessful the results may be, or have been in the past.

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8819 150TH STREET

POSTOPERATIVE PULMONARY ATELECTASIS

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POSTOPERATIVE pulmonary complications have been extensively studied and frequently reported in the literature because of their severity and high mortality. Of these, atelectasis has received much less than its deserved share of attention because of its relative benignity and its definitely decreasing incidence. The condition is of much more than didactic interest because its therapeusis is quite different from that of pneumonia or embolism, the symptom-complexes of which it may closely simulate. Prompt and accurate diagnosis is essential to the institution of proper treatment which will often preclude the possibility of septic bronchopneumonia, pulmonary abscess, chronic lobar atelectasis or other complications that arise in improperly managed cases of atelectasis.

This condition has become quite uncommon in the general run of hospital cases and, in fact, King[1] believes that "bronchial drainage either by postural change or by carbon dioxide inhalations has practically eliminated massive collapse." An indication of this decline in the number of cases is given in the following papers.

In 1914 Pasteur[2] noted it in 16 of 65 pulmonary complications after 2,000 operations. Holmes and King[3] found varying and, for the most part, minor degrees of lung collapse in 22 of 53 pulmonary complications. On the other hand, Christopher and Shaffer[4] in 1936 reported 10 cases in five years in a total of about 12,500 cases. This definite diminution in its incidence is not a little due to improved surgical technic, to the fact that anesthetics are more carefully chosen to fit the individual case, and that other prophylactic measures are more universally observed.

Peculiarly enough it occurs even less often in children excepting following appendicectomy. Of Brock's[5] 19 patients following this operation, seven were children. Accordingly, this case is reported with the hope that the diagnosis may be suspected in doubtful postoperative pulmonary complications.

CASE REPORT

The patient was a male child fourteen and one-half years old, who was admitted to the hospital on Oct. 17, 1936, with a complaint of abdominal pain and cramps followed by nausea and vomiting, of about ten hours' duration. There were tenderness and spasticity in the right lower quadrant of the abdomen and especially in the MacBurney area.

From the Surgical and Pediatric Departments, Beth-El Hospital.

The family and past history were essentially irrelevant. The only laboratory findings of importance were white blood cells 12,600 with 73 per cent polymorphonuclear leucocytes.

He was operated on soon after admission at 2:00 A.M. of October 17. One-half grain of codeine and 1/100 grain of atropine were given postoperatively. The operation took about thirty minutes and an acute phlegmonous appendicitis with acute lymphangitis was found (confirmed by pathologic reports). After the operation he was put in Fowler's position and given codeine ½ grain every four hours for pain. He vomited once a short time after the operation.

On the evening of the next day, about forty hours after operation, it was noted that the respiration increased to 40 per minute and the child became quite distressed. He complained of pain in the chest, and he was markedly dyspneic. On

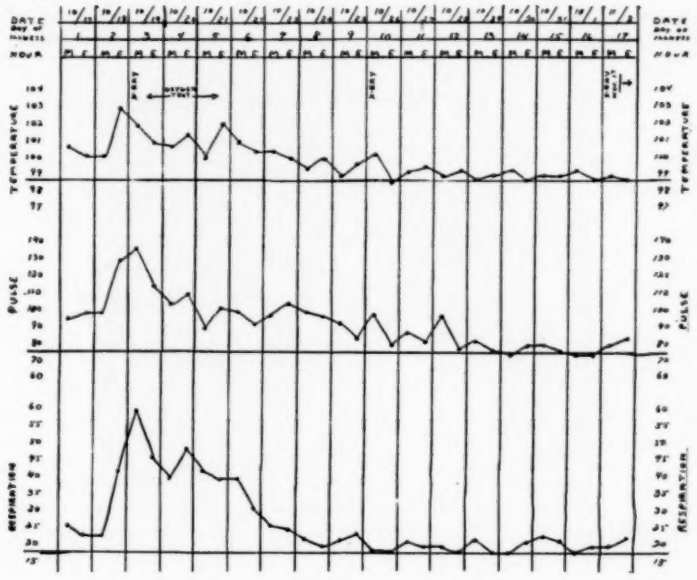

Chart 1.

examination, there was dullness and bronchial breathing in the right chest from the angle of the scapula to the base, and in the axilla. There were no râles. By the next morning (October 19), the child appeared acutely ill. Respirations had risen to 60 per minute and occasional crackling râles were heard in the right base. The findings were similar to those of the evening before, except that the heart had definitely shifted to the right, the apex could be felt and percussed in the fourth intercostal space just to the left of the sternal border. The alae nasae were dilated. The child was flushed, perspiring, definitely cyanotic. X-ray examination at this time showed absence of aeration in lower one-third of right pulmonic field limited above by interlobar fissure. Heart and mediastinum were pulled over toward the right. It was undoubtedly a case of atelectasis of the right lower lobe (Fig. 1).

He was placed in an oxygen tent, where he seemed much more comfortable. Because of his apparently extreme condition, he was not disturbed except to change his position frequently.

By the morning of October 21, about sixty hours after onset and one hundred hours after operation, the child was removed from the oxygen tent. Dyspnea and cyanosis were much diminished. The heart had moved quite a bit over toward the left side. There had been much coughing with expectoration of some viscid sputum. On this date the blood showed 8,200 white blood cells with 72 per cent polymorphonuclear leucocytes.

By October 24 the child was entirely comfortable, but there were still some signs of residual collapse (slight dullness to percussion and bronchovesicular breath sounds) on the right side.

On October 26, x-ray (Fig. 2) showed reexpansion of the right lower lobe with accentuation of the right interlobar fissure. The child rapidly improved following this with only a very slight wound infection which cleared up in a day, and he was discharged from the hospital on Nov. 2, 1936, seventeen days postoperatively.

On November 17 he returned for another x-ray examination (Fig. 3), which showed complete recovery to normal. Symptomatically, he was entirely well.

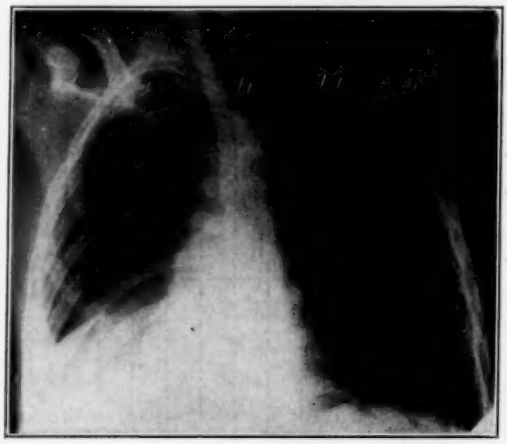

Fig. 1.—Atelectasis of right lower lobe, as indicated by the increased density in this area; the heart is displaced to the right (to the affected side).

The complication is most common after upper abdominal laparotomy, but the patient with a lower abdominal operation is by no means exempt from the possibility of its occurrence. It was shown by Muller, Overholt and Pendergrass[6] that there was a reduction of the volume of the chest in all of the twenty-five of their postoperative cases. These were all upper abdominal cases. However, this also occurs in lower abdominal operations, as shown by Churchill and McNeil,[7] Powers,[8] Head[9] and others, in that there is a marked reduction in vital capacity. This is due to many factors, such as interference with expansion because of pain, constriction by surgical dressings, and abdominal distention, all of which cause elevation and restriction of the diaphragm.

It is well known that postoperatively the chest takes the "acapnial" position, which it would assume during normal expiration. This hypo-

ventilation predisposes to pulmonary infection or atelectasis. Coryllos[11, 12] believes, in fact, that lobar pneumonia is always preceded by occlusion of a bronchus and that pneumococcic infection of the bronchial tree is not alone sufficient to cause lobar pneumonia without this collapse.

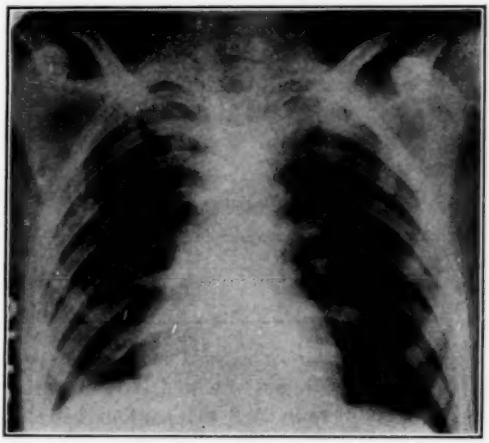

Fig. 2.—Partial expansion of right lower lobe, as evidenced by diminution in density, as compared with Fig. 1. The heart is partially shifted to its normal position.

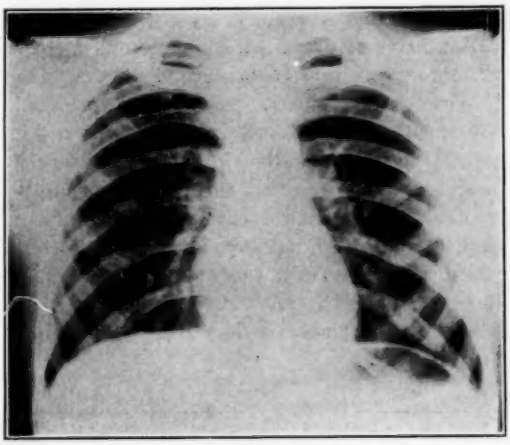

Fig. 3.—Complete reexpansion of right lower lobe. Heart has assumed its normal position.

Overholt[10] found that the normal subatmospheric pressure in the upper abdomen becomes positive in dogs after laparotomy with resulting elevation, and diminished respiratory excursion of the diaphragm. From these observations some degree of retraction atelectasis is to be

expected after abdominal operations, and it may be assumed that bronchial plugging from retained secretions may then more readily occlude already somewhat narrowed bronchi.

In the final analysis it is almost invariable that inspissated secretions or vomitus cause the actual obstruction which precedes the atelectasis.

Males are more frequently affected than females, in a striking proportion. Sixty-two (73 per cent) of Brock's 85 cases and 284 (67 per cent) of King's cases were in males.

The presence or absence of sepsis is undeniably important. A glance at Table I (King) proves that the more severe the infection, the more frequent the pulmonary complication.

TABLE I

Simple appendicectomy	6.6%
Appendicectomy with exploration	7.4%
Appendicectomy with drainage	17.9%
Appendicectomy abscesses	22.5%

Upper respiratory infection as a predisposing factor was, contrary to most authors, denied by King who stated that he could find evidence of preexisting infection in only 14.3 per cent of his cases. However, most agree that if possible to postpone an operation it should be postponed if any infection is present.

Brock is most emphatic on this point and maintains that "the fact that some cases [with upper respiratory infection] escape without a chest complication helps to prove . . . that no one factor is responsible but numerous factors working together and playing parts of varying importance."

The type of anesthesia employed is apparently a slight factor in the causation of these complications. It is surprising how the facts differ from the obvious expectation that inhalation anesthetics would be especially likely to set the stage for pulmonary complications. Brock says that "the use of inhalation anesthetics does not carry with it any increased freedom from postoperative pulmonary complications." Brunn and Brill[13] found that 62 per cent of their cases of atelectasis followed spinal anesthesia. King gives his extraordinary data (Table II).

TABLE II

TYPE OF ANESTHESIA	CHEST COMPLICATIONS (%)
Ether	12.4
Ether and spinal	18.3
Spinal	16.7
Local	18.4

However, it must be remembered that the last three types of anesthesia might have been employed more frequently in cases where other factors had increased the chance of postoperative pulmonary complication.

Atropine before and after operation is undoubtedly a factor of importance since it is known to thicken secretions which may be more likely to occlude a bronchus and may not easily be dislodged. Dehydration of the patient by illness may predispose in a similar manner.

DIAGNOSIS

The onset of the complication is most usually quite dramatic with much distress, increasing dyspnea and frequently progressive cyanosis, but comparatively little pain. The syndrome is usually well defined by the end of twenty-four to forty-eight hours after operation. The temperature and the pulse rate rise very rapidly, the latter usually disproportionately higher than the former. There is much flushing and perspiration of the face. Most often the patient tends to lie toward the affected side. There is usually a throaty cough and occasionally expectoration of a viscid sputum. This cough is due to mucopurulent secretions in the bronchi and trachea. The rusty or blood-tinged sputum of pneumonia is never seen.

Physical examination of the chest may reveal diminished expansion of the affected side, and dullness on percussion. Auscultation varies in different patients and at different times in the same patient. Typically there is absence of breath sounds and no râles, but as the obstructing secretions may change their position or permit air into some parts of the affected lobe, there may be coarse rhonchi for varying periods of time. One of the most striking signs is the shifting of the heart, always toward the side of the lesion, and often the displacement of the trachea in the same direction. It must be remembered that these signs may change, or may be masked, and that an x-ray examination should be unquestionably be performed if the least doubt exists, as it quite often does.

This x-ray study is of the utmost importance and of the greatest aid. Brock notes the following features that are seen in most cases of atelectasis.

1. The area of opacity indicating the extent of lung involvement.
2. The displacement of the mediastinal structures, heart, and trachea.
3. The crowding together of the ribs and narrowing of the intercostal spaces, giving a "roof-tile" appearance.
4. Elevation of the diaphragm if it is not obscured.
5. The diminution of the total volume of one hemithorax as compared with that of the other side.
6. The frequent appearance of patchy areas in the less affected side.

Holmes is of the opinion that those cases in which the study shows increased density with a definite diminution in lung volume on the affected side should be diagnosed as collapse. However, he cautions against making a diagnosis from a film taken at full inspiration, be-

cause at this phase of respiration displacement of the affected side is present in consolidation as well as in atelectasis.

With all these criteria to help differentiate it from pneumonia, the diagnosis seems quite simple. The one point that must be emphasized is that it should be suspected and considered.

PROGNOSIS

Generally speaking, the complication is in itself seldom of grave consequence since few die from it alone, but it must be remembered that it may be a contributory cause to death since there is the constant danger of trapping infection in that part of the lung supplied by the occluded passage, and permanent damage due to abscess and bronchiectasis. In rare instances the affected part of the lung remains permanently collapsed even though the bronchial obstruction is relieved.

However, especially with active therapy, there is complete recovery by the end of two to four days in by far the most of the cases.

PROPHYLAXIS

Whenever possible, any condition which may predispose to atelectasis should be avoided. No elective operation should be carried out in the presence of upper respiratory infection as mentioned above, or for that matter in the presence of any infection. The use of drugs like atropine and belladonna should be discouraged whenever possible, and especially where other predisposing factors are present. The patient should be well hydrated if possible. Frequent change of position postoperatively should be carried out, unless contraindicated for other reasons. Prompt relief of bowel or stomach distention should be effected, since doing so may help to diminish the elevation of the diaphragm. Binders should not be applied so as to diminish the respiratory excursion too greatly. The value of routine use of carbon dioxide inhalations postoperatively is a mooted question. Quoting many statistical studies with similar results, such as Scott,[14] Shatzky,[15] Size, Mason and Bogan,[16] Fischer,[17] Aza,[18] and others, and after comparing 1,300 operative cases of his own (one-half treated with prophylactic carbon dioxide inhalations and one-half untreated), King[3] concludes that "carbon dioxide inhalations are of no greater value in preventing postoperative pulmonary complications than frequent changes in the position of the patient."

However, Christopher and Shaffer[4] suggest the following standard routine:

> Deep-breathing exercises (ten times per hour) every waking hour for all postoperative cases.
>
> Two or three carbon dioxide inhalations every half hour to increase depth of respiration if it is shallow.

Freeing the chest of pain to encourage easy, deep respiration.

Maintenance of the cough reflex and urging the patient to cough.

Trendelenburg position for every patient who had upper respiratory tract infection prior to operation or a stormy anesthesia, or who is raising large quantities of mucus postoperatively, unless such treatment is contraindicated by the surgical condition.

TREATMENT

The most important therapeutic procedures are active effort on the part of the patient to obtain free expectoration and frequent change of posture. These are the safest and most easily instituted procedures to assist bronchial drainage. The patient may even be rolled with head over the side of the bed, of course very gently and with much assistance, and urged to cough in this position.

Christopher and Shaffer[4] have the patient lie on the uninvolved side and then he is rolled back and forth and urged to cough. They suggest that the affected side may be slapped, and that the depth of respiration should be stimulated with carbon dioxide when necessary. If these results fail, bronchoscopy is urged to remove the material which is causing the obstruction. This is rarely necessary and, of course, should be avoided if possible.

If fluid is present in the pleural cavity, it should be removed to allow reexpansion and prevent the formation of dense pleural adhesions and connective tissue within the lung, which, of course, would not permit it to return to a normal state.

COMMENT

King,[1] in attempting to evaluate the prophylaxis of pulmonary complication by the use of carbon dioxide inhalations preoperatively, made the statement that in his study he did not deem it wise "to separate pneumonia from collapse because in both, interference with respiration is at least partly responsible for the complication." This attitude should be avoided, we believe, if only for scientific exactitude, but there is also the definite reason that atelectasis and pneumonia must be treated quite differently.

Of course there are many cases which are more difficult than others to classify, and in fact are frequently impossible of diagnosis, but the attempt should be made whenever possible.

The long lists of prophylactic procedures as given by many authors are too often filled with impracticable suggestions. Certainly very few hospitals utilize the routine carbon dioxide inhalation method. Undoubtedly, too, there is little reason for such strenuous prophylaxis in such an uncommon entity.

If nothing else has been accomplished by the report of the case, it will have served its purpose if an occasional patient is saved a few hours of discomfort, and if very rarely a fatality is prevented by the fact that the complication is considered in all doubtful postoperative pulmonary conditions.

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THE TREATMENT OF PERTUSSIS WITH SPECIFIC SOLUBLE ANTIGEN

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WHOOPING cough is a disease which has challenged therapeutic approach. Many specific and nonspecific measures have been tried, but none have stood the test of time. The clinical picture of pertussis may be resolved into two components: first, the paroxysmal stage, very likely due to sensitization of the mucous membrane of the upper respiratory tract by *Hemophilus pertussis* or its products; and, second, the stage of low grade inflammation, represented by persistent hacking cough and due to secondary bacterial invasion of the respiratory tree. It occurred to Roos[1] that control of the paroxysmal stage could perhaps be best accomplished through local desensitization by means of the nasal administration of a suitable antigen solution.

That absorption takes place from the upper turbinates is a well-accepted fact.[2] Such diverse substances as diphtheria toxoid,[3] scarlet fever toxin,[4] typhoid vaccine,[5] insulin,[6] and pituitrin[7] have been demonstrated to be effective when administered intranasally.

A pertussis soluble antigen was prepared by Roos at the Mulford Biological Laboratories, Sharp and Dohme, Glen Olden, Pa. It is a bacterial antigen made from the freshly isolated, phase I cultures of *Hemophilus pertussis* grown on blood agar and harvested at the time of optimum growth before autolysis sets in. The organisms are suspended in buffered physiologic saline solution. After maceration the insoluble residue is separated by centrifugation, and the soluble antigenic substances are obtained from the supernatant liquid. The antigen is standardized on the basis of complement fixation against the specific immune serum.

Preliminary clinical reports on such a method of treatment of pertussis were encouraging. In 1935, in order to test the value of this therapeutic measure, a group of physicians in the city of Chester, Pa., were asked to use this soluble antigen in the treatment of cases of whooping cough that occurred in their respective practices.

All patients thus treated gave a definite history of exposure, and the clinical picture was definite and clear-cut. In many, positive cough plates were obtained. The treatment consisted of the nasal instillation of from 5 to 10 drops of the antigen daily, or every other day depending on the severity of symptoms and the response to treatment. The child's head was hyperextended in the dependent posture for about five minutes,

so that the antigen drops reached the surface of the middle and superior turbinates from which absorption takes place. In some of the cases, an excess of antigen (dropperful) was used to insure sufficient absorption.

CASE 1.—(Treated by Dr. W. H. Goodman.) G. L., a colored male, nineteen months old, developed whooping cough in the middle of February, 1935. When seen by the physician, he was having two or three choking spells during the day and three or four at night, with vomiting. After the first nasal instillation on March 1, there was a spectacular reduction in the number of spells. After the third treatment, he had an occasional choking spell at night, but no vomiting. The antigen was applied daily. A dry cough persisted for three weeks. The entire duration of the illness was five weeks. The results of the treatment were excellent.

CASE 2.—(Treated by Dr. W. Blair.) E. A., a white female, three years old, had been whooping for a few days when seen by the physician. One or two paroxysms occurred every hour, with vomiting after meals. Several attacks of epistaxis had occurred. Five drops of the soluble antigen were dropped in the nose every day, beginning on March 14, 1935. After the second dose the paroxysms were definitely decreased in number and severity. On March 20 she had only three coughing spells during the night. The child continued to improve, and on March 25 had a mild cough, but no paroxysms. By March 30 she was free from symptoms. The results of the treatment were good.

CASE 3.—(Treated by Dr. W. Blair.) A. A., a white female, one year old, sister of E. A., had an almost continuous cough, with one or two choking spells per hour. She whooped, vomited, and became deeply cyanotic. On March 16, two days after treatment was instituted, the paroxysms decreased in number. On March 20 she coughed most of the night, but the paroxysms were mild. She vomited once. On March 30 bronchitis with loose cough and excessive mucous secretion in the nose and throat were present, with no whooping. On April 3 the child had a severe paroxysm of coughing with rupture of a conjunctival vessel. Seven days later the patient was well. Results of treatment were fair. The recurrence of paroxysmal cough may have been due to faulty absorption of the antigen because of an excessive amount of mucus in the nose.

CASE 4.—(Treated by Dr. W. Blair.) R. J., a white male, eighteen months old, began to whoop on March 7, 1935. When he was awake, paroxysms of coughing occurred about every twenty minutes. He had four or five spells at night. After the first treatment on March 9, the paroxysms were less severe and occurred about every two hours. On March 12 four or five coughing spells occurred at night, but none during the day. The mother had difficulty in holding the child in the proper position for administering the nasal drops; on March 16 the cough became worse, and both whooping and vomiting returned. Intranasal therapy was then resumed, and on March 19 there was neither whooping nor vomiting. The cough became milder. On March 25 the patient was well. The results of the treatment were good. Because of resistance on the part of the child, treatment was stopped. There was prompt recurrence of symptoms, which were controlled upon resumption of treatment. This may indicate that the relief obtained following nasal instillation of the antigen is due to a temporary desensitization of the respiratory mucosa and that treatment must be continued until desensitization is complete.

CASE 5.—(Treated by Dr. W. H. Goodman.) R. L., a white female, four and one-half years old, began to cough on Jan. 2, 1935. She whooped and vomited during the second week, averaging two or three spells a day and ten to fifteen at night. Amytal, gr. 1, given by rectum induced sleep and reduced the number of spells to three or

four per night. On Feb. 8, 1935, the specific soluble antigen was first used. After the first two treatments, the mother reported astounding results, saying that the child no longer seemed to have whooping cough. Only a deep bronchial cough persisted. The amytal was stopped, and the child slept without it. During the early part of the third week, the mother ran out of the antigen, and paroxysmal cough and whooping recurred. Amytal did not control them, but further use of the soluble antigen brought relief. The entire duration of illness was six weeks. The results of the treatment were excellent. This case illustrates the necessity of continuous treatment to prevent recurrence, once the symptoms have abated. It also supports the theory of a local desensitization as the modus operandi of this form of therapy which must be maintained through repeated absorption of the antigen. Only the paroxysmal explosive phase of the disease falls within its sphere of action.

CASE 6.—(Treated by Dr. F. Miller.) A. C., a white male, four and one-half years old, had had a cough for ten days with severe paroxysms of whooping and vomiting for four days, when specific treatment was instituted. He had also had several severe nosebleeds. After the first instillation, the child, who had been unable to sleep, spent a comfortable night. The antigen was continued every second day. After the fourth treatment the paroxysms disappeared, and the child was able to take food. A mild cough continued for two more weeks. The results of the treatment were excellent.

CASE 7.—(Treated by Dr. F. Miller.) B. C., a younger brother of A. C. (Case 6), three years old, had a milder form of pertussis. He was decidedly improved after the first treatment; instillations were continued for the next ten days, when he became free of symptoms, except for a slight cough. The results of the treatment were excellent.

CASE 8.—(Treated by Dr. W. Blair.) R. W., a white female, four years old, began to whoop on Feb. 18, 1935. After the first few nasal instillations, the cough was much decreased and whooping disappeared. On February 25 a hard cough was still present, but there were no paroxysmal exacerbations, no vomiting, and no cyanosis. On March 5 the child was doing very well. By March 12 she was well. The results of the treatment were excellent.

CASE 9.—(Treated by Dr. W. Blair.) E. C., a white female, seven years old, was first seen on Feb. 11, 1935. She had a paroxysmal cough, vomiting at each meal, and insomnia due to choking at night. She had never had pertussis before. Medication did not control the paroxysmal cough, and, after cough plates were reported positive for pertussis, specific intranasal treatment was instituted on Feb. 20, 1935. Three days later she scarcely coughed during the day. She had only four spells at night. By February 25 the patient had not vomited for two days and did not whoop. A hard cough, worse at night, was still present. On March 5 the patient was doing well, having coughed three times the night before. On March 9 she was free of symptoms. The results of the treatment were excellent.

CASE 10.—(Treated by Dr. W. Blair.) M. C., two and one-half years old, sister of E. C. (Case 9), developed whooping cough at the same time and was treated in the same way. Symptoms were controlled by the nasal drops, but in the third week of her illness her stomach became upset, and she fought against the administration of soluble antigen; whooping and vomiting recurred. On March 5, because cooperation was poor, treatment was discontinued. Whooping persisted for several weeks. The results of the treatment were poor because of lack of cooperation.

CASE 11.—(Treated by Dr. W. Blair.) J. W., brother of R. W. (Case 8), two and one-half years old, suffered from a more severe case of pertussis but responded well to

specific treatment. Occasionally his dry cough was broken up by a paroxysm of choking and whooping. Such a recurrence usually followed interference with nasal treatment (mother could not keep the child down). The illness lasted over four weeks. The results of the treatment were good.

CASES 12, 13, 14, and 15.—(Treated by Dr. G. Blumstein, Philadelphia.) These patients were all of the same family, seven, six, four, and three years of age, respectively. There was a definite history of exposure. The two younger children had marked paroxysms of whooping. The older two had a deep dry cough. Soluble antigen was applied daily starting on Jan. 5, 1935. On January 9 the paroxysms were controlled, and only a slight cough remained. The two older children never developed paroxysmal whooping, but their dry cough did not improve under specific therapy. The results were excellent.

CASES 16, 17, and 18.—(Treated by Dr. G. Blumstein, Philadelphia.) These three children were all in the same family, six, four, and three years old, respectively. They had been exposed to pertussis and had developed paroxysmal coughs, with vomiting, lasting for over two weeks. After the third application of soluble antigen, the paroxysms disappeared and were replaced by chronic coughs, which persisted for over three weeks. The results of the treatment were excellent.

CASE 19.—(Treated by Dr. H. Gold.) P. D., a white female, aged nine months, began to cough late in April, 1935. When seen on May 10, she had been whooping severely for a week. She choked frequently and vomited most of the feedings. After positive cough plates were obtained, nasal instillation of antigen drops was begun on May 14. After the third daily treatment, she showed improvement with considerable decrease in the number and severity of spells. At the end of a week's treatment there was complete relief from paroxysms. The results of the treatment were good.

CASES 20 and 21.—(Treated by Dr. H. Gold.) Twins, aged sixteen months, had contracted whooping cough from an older brother. Paroxysms were severe, having lasted about two weeks. One of the twins vomited with each spell. On Dec. 4, 1935, specific intranasal therapy was instituted with marked improvement. After the third application the mother ran out of drops, and choking spells recurred on the fourth day. Upon resumption of treatment they subsided. After the fifth intranasal application the paroxysmal cough and choking disappeared, but a steady dry cough, which did not interfere with the children's nutrition, persisted for another two weeks. The results of the treatment were good. When the duration and severity of the paroxysmal stage in these twins are compared with those of the brother who did not get intranasal treatment, there is no doubt as to the efficacy of therapy employed.

CASE 22.—(Treated by Dr. H. Gold.) M. H., four years old, developed severe whooping cough in September, 1935. Intranasal therapy was instituted during the second week of the illness. After the fourth daily application, the whooping was controlled, with resulting disappearance of vomiting and choking. A dry cough which persisted for three weeks did not respond to the usual cough medication and change of climate (seashore). The results of the treatment were excellent.

CASE 23.—A patient with pertussis in advanced stage was treated by Dr. F. Nyemetz without any improvement.

CASE 24.—A patient with pertussis was seen in the second week of whooping by Dr. P. K. Park. Intranasal therapy gave no relief.

CASES 25 and 26.—(Treated by Dr. R. B. Loughead.) Two sisters, aged four and five years, respectively, developed whooping cough in January, 1936. Nasal

drops were administered every other day. After the fourth application there was complete subsidence of the choking and vomiting. A week later, the mother reported that both children were doing well, except for a slight dry cough. The results of the treatment were excellent.

CASE 27.—(Treated by Dr. W. Blair.) A three and one-half-year-old white girl was seen on January 25, 1936, complaining of a cold in the head and a cough. The latter became worse, and on February 3 there was definite whooping, choking, and vomiting after meals. Intranasal therapy was begun on February 4, with marked improvement. On February 8, after the fourth treatment, the paroxysms had subsided, but dyspnea, cough, and fever developed. Signs of bronchopneumonia appeared in the chest. The child was critically ill until February 18. Throughout the acute respiratory infection, the nasal administration of antigen was continued with complete control of the whooping. The results of the treatment were excellent.

CASE 28.—(Treated by Dr. A. Rozploch.) T. F., a white female, fourteen months old, was seen the first week of March, 1936, when she was having severe whooping, strangling and vomiting spells. She began to cough during the last week of February. Treatment with intranasal antigen instillation was begun in the third week of the illness. After the third instillation choking and vomiting ceased. The patient slept most of the night and appeared comfortable. Within a week the whooping stopped, but a deep bronchial cough persisted for two more weeks. An older child, who was not treated with the soluble antigen, had a very severe form of pertussis which lasted for almost nine weeks. The results of the treatment were good.

CASE 29.—(Treated by Dr. H. Gold.) A white girl, two years old, was seen on April 10, 1936, in the fourth week of her illness. She had been whooping for two weeks, with strangling and vomiting after each meal. There was marked loss of weight, and the child appeared worn out from disturbed sleep. Because we desired to test the efficacy of the soluble antigen when given subcutaneously (nontoxic in doses of 1 c.c. when given to adults), she was given 0.1 c.c. of the antigen hypodermically without any local reaction. The next day she received 0.2 c.c. On this night she appeared to be more comfortable and slept rather well, having only three spells of whooping. No treatment was given on April 12, and on this night, she had five or six severe spells of choking. On April 13 she received 0.3 c.c. of the antigen, after which the spells decreased in number and severity and the child vomited only once. The condition remained the same until April 15, when she received 0.3 c.c. After this the child steadily improved. She whooped occasionally, and on April 18 she was given 0.4 c.c. of the soluble antigen. Her condition remained unchanged, and a week later she received a second dose of 0.4 c.c. Within a few days she became free from symptoms. There was no reaction at the site of injection at any time. Some improvement occurred after the subcutaneous administration of this antigen, but whether it was due to it or to a spontaneous natural improvement is difficult to say since treatment was begun rather late in the course of the disease.

CASE 30.—(Treated by Dr. H. Gold.) A white boy, aged four years, brother of the patient in Case 29, was seen on April 15, when his mother stated that he had been coughing for about two weeks. The cough was nonparoxysmal and was associated with expectoration of a small amount of yellow mucus. He had choked and vomited for the first time on the morning of the fifteenth. A differential blood count taken then was typical of pertussis. Cough plates revealed the presence of *H. pertussis*. One-tenth cubic centimeter of soluble antigen was given subcutaneously on April 15. During that night he had one coughing spell. Then 0.2 c.c. of the antigen were given on April 16. Two days later the mother stated that the

child had been coughing very lightly once or twice at night. There was no whooping, no choking, no vomiting. Three-tenths cubic centimeter of antigen was then given. On April 21 the child appeared to be in good health. He coughed occasionally but very lightly. A dose of 0.3 c.c. of antigen was given in the left arm. On April 24 there was hardly any cough. The mother had to be begged to bring the child to the office. Three-tenths cubic centimeter of antigen was given in the right arm. The results of the treatment were excellent. Duration of illness was less than three weeks. This child never suffered any of the distressing manifestations of the paroxysmal phase of pertussis, and the very mild short-lived course of the disease is in sharp and striking contrast to that of the sister (Case 29), which was the original source of infection in this household.

DISCUSSION

Of the twenty-eight cases of whooping cough treated intranasally with the specific soluble antigen, 17 (60.7 per cent) responded with excellent results to this form of therapy. In seven additional cases good results were obtained. When these two groups are combined, we may state that in 85.7 per cent of the cases treated very satisfactory control of the severe paroxysms of cough resulted following the use of this antigen. In one case the antigen appeared to be of some help. In three cases it was of no value.

Although our series is small, we feel that we have in this antigen a valuable aid in the treatment of pertussis. Similar results have been reported by Slesinger.[8]

The therapeutic effect of the antigen seemed to be limited to the paroxysmal stage of the disease and did not affect the nonparoxysmal cough present in pertussis. In this regard, attention should be drawn to the fact that it is the paroxysmal phase of whooping cough which most severely affects the health of these patients. In our experience, its control produces a startling change in the clinical picture of the children we have treated with the soluble antigen. It also appears to shorten the duration of the disease.

We believe that the modus operandi of this form of therapy is desensitization. This conclusion is based upon the fact that only the paroxysmal spasm and cough are controlled by the antigen and that the maintenance of relief depends upon frequently repeated administration of antigen. Otherwise recurrence of whooping is prompt.

To test further the specificity and mode of action of the soluble antigen, we administered it subcutaneously to two children (Cases 29 and 30). In case 30 the child, who was seen early in the disease, about two weeks after the onset of the cough and who had a typical blood picture and positive cough plates, never developed whooping, choking, or vomiting, following specific treatment. The entire illness lasted less than three weeks. When one compares his record with that of his sister (Case 29), who was treated late in the disease, one is struck by the change in the course of pertussis brought about by this antigen.

Frawley, Stallings, and Nichols,[9] using Krueger's undenatured pertussis vaccine in the treatment of whooping cough, found it necessary to administer hypodermic injections at frequent intervals to maintain the relief obtained and postulated local desensitization as the modus operandi of their form of therapy.

This soluble antigen, found to be safe, gave no untoward reactions locally or systemically when given in large doses, either intranasally or subcutaneously. Either method can be used with advantage in the treatment of whooping cough.

The merits of each are obvious. The intranasal method appeals to us because of its ready applicability, requiring, however, good technic. The variable and uncertain factor is that of absorption. Extrinsic elements, such as mucus in the nose, will hinder its absorption and prevent desensitization. This variability is not present when the antigen is given by the subcutaneous route. The latter, however, requires the hypodermic needle, with its bad psychologic effects, especially on children.

CONCLUSIONS

1. A specific soluble pertussis antigen has been prepared from phase I *Hemophilus pertussis*. The antigen is chemically and biologically standardized.

2. This soluble antigen can be given safely without untoward reactions to children suffering from whooping cough either by intranasal or subcutaneous routes.

3. Thirty children suffering from pertussis have been treated with this soluble antigen. Clinical records and results of treatment are given.

4. The soluble antigen specifically controls the paroxysmal stage of whooping cough. Relief is obtained after the first few treatments. To maintain relief and to prevent recurrence, treatment must be maintained. The earlier the treatment is instituted, the better are the results obtained.

5. We feel that this specific soluble pertussis antigen will prove to be a valuable adjunct in our therapeutic armamentarium.

I wish to express my appreciation to my colleagues who treated these cases of pertussis for permission to publish the results obtained.

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THE EFFECT OF REPEATED BLOOD TRANSFUSIONS UPON THE ERYTHROCYTE SEDIMENTATION RATE IN RHEUMATIC HEART DISEASE

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IN THE last few years the literature has been replete with articles discussing the value of the erythrocyte sedimentation rate as an indicator of progress in various pathologic states. Some of the authors seem skeptical of its usefulness; notably among these are Simunich[1] and Williams,[2] who in their studies of gynecologic patients did not find the test a reliable guide. Also Peterman and Seeger,[3] working with infants and children, and Buchanan,[4] in his observation of a group of adults, came to the conclusion that the relationship between high readings and disease manifestations is indefinite. Most writers on the subject, however, are enthusiastic about the diagnostic value of the test and believe it to be highly significant.

Observations so far establish certain facts of application. Although the sedimentation rate is not a specific diagnostic test of one disease any more than is an elevated temperature or an increased leucocyte count pathognomonic, nevertheless, when properly evaluated, it indicates the presence, the absence or persistence of infection, the activity of the disease process, and it has proved of value as a gauge in estimating the progress of the illness, as an indicator of complications and as a reliable guide in respect to the efficacy of the treatment. Furthermore, a slowing or acceleration of the sedimentation rate may be a substantial factor in differential diagnosis. Hirsh[5] has made an excellent and comprehensive review of the literature together with the historical background of the test. In 488 sedimentation tests which he performed on 395 patients the results confirmed its reliability.

In the field of pediatrics its greatest usefulness has been generally recognized as a means of following the course and activity of febrile infectious disorders. In such cases it has proved valuable as a prognostic agent. Whether the therapeutic measures employed are effective or not is also indicated, for clinical improvement and slowing of the sedimentation rate synchronize as do an unfavorable course and increasing rapidity of sedimentation.

The test as applied especially to rheumatic fever and rheumatic carditis offers most interesting and enlightening information. In an extensive review of reports and discussions on the particular subject, Hench and his coworkers[6] stated: "Further evidence is given that changes in the sedimentation rate are almost parallel with the varied

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progress and clinical alterations of this disease. The test distinguishes between a false improvement due perhaps to salicylates and one due to recession of the disease. It provides a numerical gauge to the patient's progress, good or bad. Its persistent failure to return to normal when fever and joint pains subside is highly suggestive of the continued presence of active pathologic changes such as a cardiac lesion." These same authors,[7] in a review of subsequent literature, found that previous opinions on the sedimentation rate have been confirmed, namely, that it is elevated in rheumatic fever and rheumatic carditis; it varies with the activity of the disease and affords one of the most delicate gauges of activity. Stainsby,[8] concurring in this view, likewise claimed that in rheumatic fever the sedimentation index, employed in conjunction with the temperature records and the Schilling differential white cell count, provides the clinician with additional aid in determining the activity and course of this important disease. It is his opinion that a case of rheumatic fever should not be considered inactive unless these three indices have returned to normal.

Furthermore, the test is regarded of value in checking the efficacy of treatment. Concerning this phase, Payne[9] directed attention to an interesting point in discussing Sheldon's three cases of acute rheumatic fever in which aspirin was given and the patients appeared clinically to have been benefited by the drug although a study of the sedimentation rates revealed that there was no slowing in the settling of the erythrocytes.

Some pertinent facts were brought out in a report by Rogatz,[10] which contained the study of twenty-five children with acute rheumatic fever, some having cardiac involvement. In these cases the Schilling blood count and sedimentation rate were compared. He concluded from his work that the sedimentation rate shows greater sensitivity as an index of inactivity in rheumatic infection than the Schilling count, and as a result of his observations he advocated the use of the former as a guide to determine when convalescence from this disease has been completed. Clifton,[11] in a recent article, was of the same opinion concerning the comparative value of the two tests and found that the sedimentation test is more reliable than the Schilling differential count in the diagnosis of the activity of the rheumatic process.

If one shares the opinion that the sedimentation rate is indicative of the degree of activity of infection in rheumatic fever, then the following report of a case in which blood transfusions were used as a remedial agent will to them be of considerable interest.

CASE REPORT

History.—The patient, C. P., aged nine years, was admitted to the pediatric ward of the Newark Beth Israel Hospital on April 19, 1936, the diagnosis being acute rheumatic carditis. This was his sixth attack. His first one occurred at the age of five years and lasted eight and a half months. Like this present episode it began

in April. Following the last attack, he was sent to a local cardiac convalescent sanatorium, at which place he did well. This past year he was at home and attended our cardiac clinic in the dispensary. There is no history of rheumatic disease in the family. His previous personal history other than the recurring attacks of rheumatic fever is not significant. His tonsils were removed after the first attack. The fifth relapse was so severe that his recovery was continually in doubt. The present illness began a week prior to admission beginning with a sudden rise in temperature, vomiting, severe headache, cough, precordial pain, dyspnea, palpitation, and pain in both ankles. Because of the continuance of these symptoms, he was brought to the hospital.

Physical Examination.—A white boy, rather stout in appearance, was sitting up in bed. He was having difficulty in breathing, was extremely restless, and was obviously in distress. His lips were cyanotic, his temperature was 103.2°, the respiratory rate 24, and the pulse rate 140. The blood pressure was systolic, 90, and diastolic, 60. His fingernails and toenails were cyanotic. Both ankle joints were swollen, puffy, and painful; no other joints were involved. The veins of the neck were bulging and pulsating. Examination of the chest revealed the apical impulse displaced outward to within ¾ inch of the anterior axillary line. There was a diffuse rippling precordial impulse. There was an increase in the area of cardiac dullness both to the left and right. The heart sounds were feeble and embryonic in type. Because of the rapid heart rate it was impossible at the time to interpret the murmurs with any degree of accuracy. A suggestive pericardial friction rub was heard at the base. The lungs were negative except for crepitant râles at the right base. The liver and spleen both were enlarged. There was no ascites.

Blood count: Erythrocytes, 4,240,000; hemoglobin, 84 per cent (14.5 gm. per 100 c.c.); leucocytes, 11,500; segmented neutrophiles, 69 per cent; nonsegmented neutrophiles, 7 per cent; lymphocytes, 16 per cent; monocytes, 7 per cent; and basophiles, 1 per cent. Blood sedimentation rate was 127 mm. in first hour and 129 mm. in second hour (Linzenmeier method). Urinary findings were negative. Wassermann and Kahn tests were negative.

The diagnosis was acute rheumatic heart disease.

Course and Treatment.—After admission to the hospital the child became progressively worse, developing signs of cardiac insufficiency and later of pericarditis. His breathing was so embarrassed that it was necessary to give symptomatic relief by placing him in an oxygen tent. At this time he was very feverish and appeared desperately ill. He remained in the oxygen tent for a period of two weeks, experiencing considerable relief. The patient improved to the point where he was able to do without it. However, within a short time after his removal his course became unfavorable, a pericardial effusion developed, the temperature ranged between 102° and 104° F. for weeks. Precordial pain was intense. He complained of severe pains in the knees and wrists. The circulation began to fail; the blood pressure dropped; and the eyelids and the extremities became edematous. He was orthopneic and troubled with a severe cough. The lungs showed signs of chronic passive congestion. The liver was much enlarged. The urinary output was markedly diminished. Repeated blood cultures taken at frequent intervals were all negative.

However, on June 20, nine weeks after admission to the hospital, there was a change in the course of events. The boy showed improvement for the first time, voluntarily expressing subjective relief from pain and distressed breathing. At the same time the edema disappeared, the cough lessened, and there was evidence that the pericardial effusion was subsiding and circulatory compensation returning. The temperature diminished, not rising above 102° F. in the evening. The pulse rate at this time was 140; the systolic blood pressure, 110, and the diastolic, 70; the sedimentation rate, 115. Another blood culture proved negative.

Improvement seemed to continue, but very slowly. The treatment consisted of absolute rest, a high vitamin diet, and administration of salicylates. He seemed

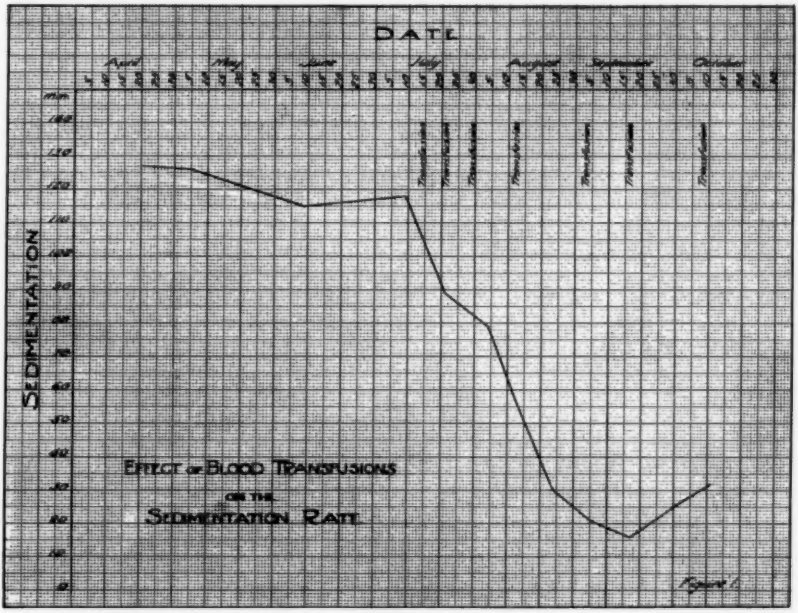

Fig. 1.

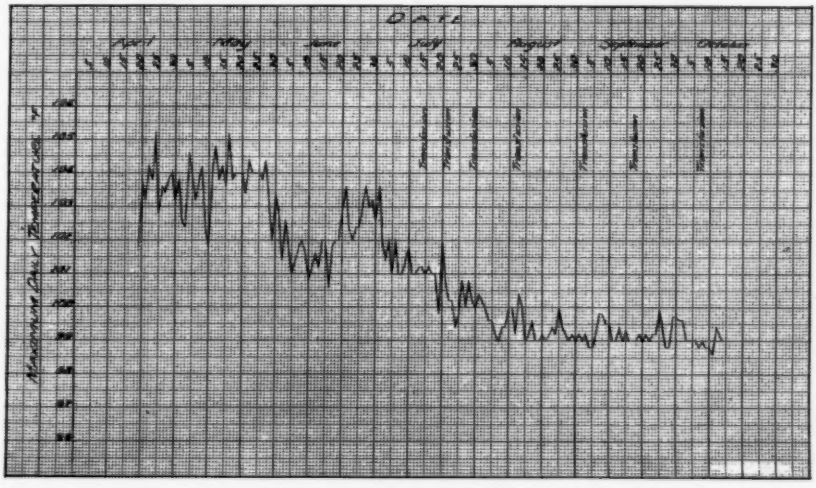

Fig. 2.

quite comfortable, but, nevertheless, the outstanding unfavorable sign to date, that is, the first week in July, was the continuation and persistence of the elevated temperature, which still showed an evening rise to about 102° F.

At this time, because of the persistent fever and the failure of the sedimentation rate to show any tendency of slowing up, as noted in Fig. 1, and because of lack of response to the vitamin diet or to the salicylates, these measures were discontinued, and the transfusions were resorted to. Accordingly, on July 15, 1936, the first transfusion consisting of 100 c.c. of blood was given by the direct method. Following this there was no reaction. Just prior to this first transfusion the sedimentation rate was 118 mm. and the blood picture was as follows: Erythrocytes, 3,900,000; hemoglobin, 68 per cent; leucocytes, 8,350; segmented neutrophiles, 71 per cent; nonsegmented neutrophiles, 1 per cent; lymphocytes, 19 per cent; monocytes, 5 per cent; and eosinophiles, 4 per cent.

On July 21, the sedimentation rate slowed down to 89. Encouraged by the result we decided to continue the transfusions. In all, seven direct transfusions were given, each consisting of 100 c.c. of blood with the exception of one, which was of 150 c.c. The apparent effect of these transfusions on the sedimentation rate is graphically represented in Fig. 1. The change in the temperature curve is also of interest, as shown graphically in Fig. 2.

Along with these laboratory indications of improvement, there was simultaneous clinical improvement, with evident subjective relief of pain and distress. The patient became quiet and cheerful, and his appetite was good. Gradually he was able to get out of bed and walk about without shortness of breath. As time went on, he was bright, happy, and alert, and his outward appearance was that of a healthy child.

Just previous to discharge from the hospital examination of the heart revealed considerable diminution in all diameters, as was shown by means of comparative roentgenograms although by auscultatory examination there was a loud rumbling crescendo presystolic murmur. The electrocardiogram recorded normal mechanism and normal sinus rhythm. There was no distention of the cervical veins, nor cyanosis nor any evident signs of pulmonary congestion. The liver had receded. The pulse rate averaged 80 and the respiratory rate, about 20. The temperature had been normal for a considerable period. The systolic blood pressure was 116 and the diastolic, 74. The sedimentation rate was down to 32. Blood count: Erythrocytes, 4,800,000; hemoglobin, 82 per cent; leucocytes, 8,050; segmented neutrophiles, 45 per cent; nonsegmented neutrophiles, 6 per cent; lymphocytes, 34 per cent; monocytes, 7 per cent; eosinophiles, 6 per cent; basophiles, 1 per cent; and myelocytes, 1 per cent.

DISCUSSION

The statement may be definitely made that no disease of childhood is more discouraging to treat than rheumatic heart disease. It would therefore seem that any method of treatment having any scientific basis to warrant its use should receive serious consideration. The pediatric literature has little to offer in the way of therapy. It is hardly necessary to point out the futility of any of the present-day therapeutic methods at our disposal, but mention may be made of those in vogue merely to emphasize our helplessness in combating rheumatic heart disease. Particularly ineffectual is salicylate therapy, the course of the disease being uninfluenced by its use. The ineffectiveness of this drug upon the pathologic process has been attested by many authors, among them being Master and Romanoff,[12] Perry,[13] Eason,[14] and Kaiser.[15] Not only were Poynton's[16] experiences with salicylates disappointing, but it is his belief that the use of the drug may actually be harmful.

In the case herein reported the problem that presented itself and the factors that indicated the giving of blood transfusions as a rational procedure were the following: The boy had had a persistently high temperature for twelve weeks with no prospect of terminating, but he had also showed a persistently accelerated sedimentation rate. The evidence was consequently clear that the rheumatic infection was active and severe, and that his physical powers in turn were ineffectual in combating the condition successfully. Since the value of blood transfusions in treating other infectious processes is undisputed and since the progress in this case appeared hopeless, it seemed justifiable to employ this mode of therapy as a possible aid to the child in overcoming the rheumatic infection. All other remedies were discontinued when the blood transfusions were instituted.

Six days following the first transfusion, the sedimentation rate lessened from 118 to 89. This effect was so encouraging that a second transfusion was given, which was again followed by a slowing of the sedimentation rate. Because these transfusions apparently were serving to combat the infection and because of the fact that they caused no reaction, they were continued at frequent intervals until the infection appeared to have become quiescent.

The temperature response was not so immediate as was the sedimentation rate. There was no decided drop until after the third transfusion. An elevated temperature frequently persists after an acute attack of rheumatic fever has subsided, indicating, of course, that the disease is smoldering on. In view of this fact the steady, even normal temperature following the series of transfusions in this instance gave the impression that the infection had quiesced to a greater degree with this mode of therapy than it had under the influence of salicylates.

Little has been written on the use of transfusions in rheumatic fever. Quite a few authors, however, have resorted to blood transfusions in rheumatic arthritis, such as Bach,[17] Ray,[18] Hoche,[19] and Copeman.[20] Some, as Abessalomoff,[21] and Khokhlov,[22] employed autohemotherapy in an attempt to treat acute rheumatism; Karp[23] used the same form of therapy on a series of patients with rheumatic arthritis. In a case of acute rheumatic fever that was not progressing well, Masselot and Bloch[24] gave repeated graduated injections of whole blood from a patient who had recovered from an attack of the disease. In this instance the authors recorded that a sudden and permanent improvement followed the fourth injection of blood.

An interesting case was cited by Fleming and his coworkers.[25] A woman, aged thirty-seven years, who suffered from acute rheumatic fever, had been in the hospital from May 13, 1924, until July 12, 1924, without signs of improvement. On this date she was given a transfusion of 500 c.c. of blood. The patient recovered so rapidly that on July 31 she was out of bed. However, it should be noted that on July 7 she had been given 10 c.c. of polyvalent antistreptococcal serum,

and, furthermore, on the same day just a few hours before the transfusion the donor had received an injection of *Staphylococcus aureus* vaccine. It was the opinion of the authors that possibly the polyvalent antistreptococcal serum may have contributed to the patient's recovery, but the chief credit was given by them to the immunotransfusion.

Knoll[26] reported the case of a patient, aged thirty-eight years, with acute rheumatic fever, who when moribund was given 500 c.c. of citrated blood. The author stated: "The patient rallied for a few hours after receiving the transfusion but then began to fail and died in cardiac collapse the next morning." In a series of pediatric cases in which citrated blood was used subcutaneously for various disorders, Moore and Dennis[27] applied the method in one case of "purpura rheumatica" resulting in recovery. No details of the case were given. Lyon,[28] in an article on rheumatic heart disease in children, found that, when the hemoglobin falls to 50 per cent or below, the use of periodic blood transfusions of 100 to 200 c.c. may be followed in many instances by marked improvement. In discussing the value of blood transfusions in the treatment of chronic diseases and the question of the expense of hospitalization, Chafee[29] made the statement that to those of us who have seen patients with rheumatic fever in an apparently stationary state suddenly improve as a result of transfusion, it is not necessary to prove that the procedure is cheaper in the long run.

A favorable result following transfusions was reported by Weiss[30] in the case of a man, aged twenty-eight years, having rheumatic fever with cardiac involvement and rheumatic pneumonitis accompanied by high temperature. His condition was considered almost hopeless at the time when the first blood transfusion was decided upon. Two hundred cubic centimeters of citrated blood was given to the patient by the drip method on March 4, 1935. Three days later a second transfusion was given, following which the temperature began to drop. The author observed that coincident with the drop in temperature the patient improved remarkably and that from this time on, the improvement was progressive. The temperature, however, continued between 99° and 101° F. for six weeks, at the end of which time, on April 20, 1935, a third transfusion was given. After this transfusion the temperature fell to normal, and ten days later the patient was discharged from the hospital.

It would seem advisable to establish the fact that the sedimentation rate is normal in all donors used in cases of rheumatic fever, as a check on their individual health. In the patient here under consideration this precaution was taken only in the selection of the last donor and not in the others.

This report deals solely with the effect of repeated transfusions on the sedimentation rate in a case of rheumatic carditis. It does not

intend to infer that transfusions in themselves may be a specific cure for rheumatic fever. The course of this disease is recorded as an interesting observation, with the hope that the method will be given further thought and trial, and its use will possibly open up an avenue of attack on this disease.

The primary purpose of reporting the case is to present clinical and laboratory evidence of improvement which justifies the conclusion that the transfusions were of therapeutic value. While no hope of benefitting the damaged heart valves or restoring the myocardium to normal by blood transfusions is entertained, it is my belief, based on the outcome in this case and in the others referred to, that giving blood transfusions may be a method of suppressing an attack of rheumatic fever.

SUMMARY

The case of a boy, nine years old, having his sixth attack of rheumatic heart disease is herein reported. After twelve weeks of continuous fever and a persistent accelerated sedimentation rate with no prospect of the infection subsiding, repeated blood transfusions were given and as a result of their use there apparently occurred an immediate slowing of the sedimentation rate and a drop in temperature, accompanied by clinical improvement.

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PERIPHERAL NEURITIS DUE TO LEAD

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HIPPOCRATES in the third century before Christ was probably the first of the ancients to recognize that lead might cause serious poisoning, for he described a severe attack of colic in a metallurgist. Nikander,[1] Greek poet, physician, and grammarian, in about 200 B.C., gives us, however, the earliest picture of plumbism with encephalitis and paralysis:

> Phantastic forms flit now in front of his eyes
> While deep from his breast there soon issue sad cries.
> Meanwhile there comes a stuporous chill.
> His feeble limbs droop and all motion is still.
> His strength is now spent and unless one soon aids
> The sick man descends to the Stygian shades.

Much later, in A.D. 1542, Paul of Aegina[2] for the first time clearly distinguishes between the cerebral and the neuritic symptoms, and it is interesting to note that even at this period the author has discovered that sensation is usually unaffected: "In many cases it passed into epilepsy, to some there came loss of motion, with sensation unhurt, to many both, and of those who fell victims to the epilepsy, very many died. Of those indeed who were paralyzed, not a few recovered."

François Citois[3] in 1616 described graphically the picture of lead poisoning but ascribed the etiology to bile in his discussion of "the new and common painful bilious colic at Poitiers." The predilection of lead for the extremities and the motor arc is expressed in the statement: "The motion of his elbows and hands, legs and feet is lost, sensation however is intact."

John Huxham (1738), Theodore Tronchin (1757), and Sir George Baker (1772) successively described the syndrome at greater length and ascribed its cause definitely to lead.

In 1848 Tanquerel des Planches[4] devoted a chapter to "Lead Anesthesy" in his epochal monograph on plumbism. Peripheral neuritis is described in detail, and the author notes striking sensory changes in only eleven out of his series of 1,493 cases.

Since Tanquerel's time we have had a voluminous literature describing the syndrome of plumbism with peripheral neuritis. Interestingly enough, most of the articles describing lead neuritis have been based on

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adult material, and we find very few case reports of the condition as seen in childhood, if we exclude the cases of paralysis intimately associated with active encephalitis.

Turner[5] and Gibson[6] are among the few authors who comment on peripheral neuritis in childhood, mentioning wrist-drop and foot-drop and ascribing the greater frequency of the latter to the more marked fatigue of the legs in the growing child.

Aub and his associates[7] in 1925 published the most recent complete monograph on lead poisoning and devoted several pages to a description of palsy.

Thomas and Blackfan[8] (1914), Blackfan[9] (1917), Holt[10] (1923), Ruddock[11] (1924), and McKhann[12] (1926) are American authors who, by case reports and their discussions, have acquainted the profession with the syndrome of plumbism as it is commonly seen in infancy and childhood. Vogt[13] in 1930 was the first to direct attention to the diagnosis of lead poisoning by means of x-ray examination of the ends of the long bones. In all of these articles, however, the encephalitic picture is stressed, and paralysis is usually considered as an accompaniment of cerebral rather than peripheral pathology.

From the literature, we should judge, therefore, that peripheral neuritis due to lead is an affliction encountered not infrequently in the adult group, but seldom seen in childhood in which the encephalitic picture predominates. From the literature we should judge also that disturbances of sensation rarely accompany motor weakness, at any age.

Goodwin[14] of Johns Hopkins in 1934 described a case of extensive peripheral neuritis due to lead in a three-and-one-half-year-old colored girl who had marked sensory as well as motor changes. He also noted the infrequency of neuritis in the plumbism of childhood, as compared to encephalitis. In Goodwin's case there was "complete flaccid paralysis involving both legs, both arms, the trunk muscles up to the chest and diaphragm," and "complete anesthesia to touch and pain over the whole trunk and all four extremities." Terminally the child developed convulsions and hyperpyrexia, and autopsy revealed marked myelin degeneration of the peripheral nerves, with the most striking changes in the nerves of the leg. "No change, except possibly a slight atrophy, was found in the muscles themselves. The brain showed no change, nor did the medulla, spinal cord, anterior roots, posterior roots or spinal ganglia."

Because of the relative infrequency of uncomplicated peripheral neuritis with sensory changes due to lead in childhood, we wish to describe a case seen at the Columbus Children's Hospital.

CASE REPORT

On Jan. 18, 1936, an eighteen-month-old female infant was admitted to the emergency room in a generalized convulsion which had persisted with only short

interruptions for the three days previous to admission. The baby expired within a few minutes after entry, and necropsy and x-ray examination were refused by the parents, although the possibility of plumbism was suggested to them.

Three days later, on January 21, the three-year-old sister of the deceased infant was brought to the hospital with complaint of paralysis of the hands and legs of about two weeks' duration.

The patient's mother and ten siblings were living and well. The father suffered from rheumatism, and an eighteen-month-old sibling had just died in epileptiform convulsions. There was no history of familial disease.

Fig. 1.

Past history showed the mother's pregnancy uneventful and was followed by a normal, spontaneous delivery at full term. Birth weight was 8 pounds 6 ounces, and there were no postnatal disturbances. The baby thrived on the breast and continued from the age of six months to do well on cow's milk. Her history revealed that she was largely on a diet of milk, still given by bottle, and fried foods, with very few cereals, fruits, and green vegetables.

A marked story of pica was also elicited. The patient and her deceased sister both chewed the paint off of lead pencils and from their crib, which had been freshly painted. This perverse appetite necessitated the taping the hospital crib, from which our patient also attempted to chew the paint.

Physical examination at entry revealed a three-year-old white baby girl, very irritable and noncooperative, but not acutely ill. She showed a definite wrist-drop and foot-drop and was unable to stand or to grasp objects. Her skin was dry and pale with slightly poor turgor although her nutrition seemed fairly good. Complete examination, except for extremities, revealed the following abnormalities: slight rhinitis with mucopurulent discharge; lips excoriated, dry, and fissured; several carious deciduous teeth; slight gingivitis with a definite lead line over the lower central incisors; slightly hypertrophied and injected tonsils. Extraocular move-

Fig. 2.

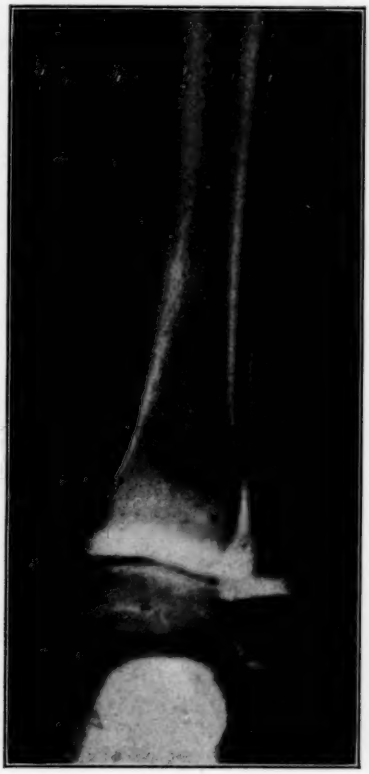

Fig. 3.

ments, reactions to light and accommodation, and fundi were not remarkable. There was no Macewen's sign, stiff neck, or Kernig or Brudzinski reflex.

The upper extremities, however, revealed a definite wrist-drop with the fingers held in flexion and apparently flaccid. The child was unable to grasp any objects. The lower extremities showed likewise a flaccid paralysis with definite foot-drop. Motion was obtained only through the psoas and hamstring muscle groups.

Examination of the reflexes revealed that the biceps and triceps jerks were slightly exaggerated. Periosteal, abdominal, knee jerk, and tendo achillis reflexes were not obtained. Attempts to elicit Babinski, Gordon, and Oppenheim reflex resulted in neither flexion nor extension on stimulation.

Sensation to touch and pain was markedly diminished over the extremities, the trunk being uninvolved. Cranial nerves were not affected.

On admission the urine showed a few hyaline casts and leucocytes, which disappeared after the first week in the hospital.

Red blood count was 3,800,000 with a hemoglobin content of 60 per cent. There were 9,200 white cells with 71 per cent polymorphonuclears, 20 per cent lymphocytes, 6 per cent monocytes, and 3 per cent eosinophiles. Basophilic stippling was noted in approximately one red cell per high power field. Blood calcium was 9.9 mg.; phosphorus, 4.6 mg. The blood Wassermann reaction was negative.

The spinal fluid showed a negative pleocytosis with the faintest possible trace of globulin.

Roentgenologic examination revealed lines of increased density at the ends of the long bones.

In view of the history of pica, with ingestion of lead, the lead line in the gums, the presence of basophilic stippling of the red cells, and the finding of the characteristic lead line in the long bones by roentgenologic examination, a diagnosis of plumbism with peripheral neuritis was made. The treatment instituted consisted of a well-rounded diet, adequate vitamins, phosphorized cod liver oil and viosterol, and dicalcium phosphate.

Recovery of function was very slow at first, and the child's appetite remained erratic. In view of the history of an inadequate diet and the possibility of associated avitaminosis, particularly in vitamin B, intramuscular liver extract was given twice a week, and a concentrated vitamin B preparation three times a day.

During the third week in the hospital, shortly after beginning the liver and the vitamin B therapy, the appetite improved markedly, and both strength and sensation in the involved extremities showed a beginning return to normal. Probably the improvement in appetite and diminution of neuritis were coincidental, but it is interesting to speculate on the possible rôle played by avitaminosis in this case.

Muscle examination and electrotherapy were carried out at periodic intervals by Mrs. Hardin, the hospital physiotherapist, and her initial report, one week after entry, reads:

"Electrical stimulation by Morton Smart unit is as follows:

"Anterior crural nerve or femoral, active to division (saphenous branch).

"Sciatic nerve, active to division at popliteal space.

"Muscles innervated by external and internal popliteal nerves and their branches, negative.

"Active response to Erb's point; below elbow, muscles innervated by median, ulnar, and radial negative with exception of wormlike contractions."

At weekly intervals, examinations were repeated which showed increasing reaction to electrical stimulation in the involved extremities, coinciding with the clinical improvement.

One month after entry the patient attempted to use her hands and to stand in her crib. Sensation was now apparently normal, and the tendon reflexes of the lower extremities had returned, except the Babinski—stimulation failing to evoke any response.

Two months following entry, the wrist- and foot-drop were much less marked, and the child was able to hold objects clumsily in the hands and could walk about the crib.

Approximately three months after admission the patient was allowed to walk with shoes. The balance was maintained fairly well except that the gait was with a wide base, the eyes were kept fixed on the ground, and the slapping of the soles to the floor before the heels indicated residual foot-drop. The wrist-drop was less pronounced, and the use of the fingers had returned almost to normal. Electrical

examination showed marked improvement over all previous examinations, with fairly normal response except in the thumb muscles which remained for the most part negative, with an associated atrophy of the thenar eminences.

The patient was discharged home about three months after entry, and return examinations to the dispensary indicated slow but consistent improvement in motor function. Some wrist-drop persisted and the thumbs were still inactive to electrical response with the exception of flexion at the distal joints. The gait was steadier, but the feet were still slapped down, though to a less degree.

On June 19, 1936, the girl was readmitted to the hospital with a story of "a light convulsion" one month previously and the sudden onset of coma and a convulsion approximately one hour before entry. Her general condition had remained good, with progressive decrease of her neuritic symptoms since discharge two months before.

Readmission showed the picture of a typical encephalitic syndrome with several generalized convulsions, probably precipitated by an acute upper respiratory infection that was present. Basophilic stippling of the red cells was again marked, and lumbar puncture this time revealed 88 cells with 98 per cent lymphocytes, and 1+ Pandy reaction. Sedatives were given and a high vitamin B and D regime with dicalcium phosphate was ordered. Convulsions soon ceased, and the temperature, which had risen to 102° F., returned to normal. Repeated roentgenograms showed a persistence of the bands of increased density at the ends of the long bones, of approximately the same width as before. Neuromuscular examination at time of discharge on June 29, 1936, was essentially the same as on the previous visit to the dispensary, and all encephalitic symptoms had disappeared.

DISCUSSION

It is not in the province of this paper to discuss exhaustively the syndrome of lead poisoning, although a brief résumé of present-day ideas appears worth while.

By far the commonest mode of absorption of lead is from the gastrointestinal tract, and in older infants and children this is usually the result of "pica," a perversion of appetite in which the child eats and chews upon all variety of foreign objects. The lead paint of cribs or beds, window sills, and toys, and "lead soldiers" appear to be favorite objects for these perverted appetites. Drinking water carried through lead pipes, lead nipple shields, and various ointments containing lead acetate applied to cracked nipples are less common means by which lead is ingested. From Japan[15] have come also reports of epidemics of plumbism in infants whose mothers used large amounts of cosmetics containing lead. Absorption is possible through the respiratory tract also, and several cases[16] occurring as the result of burning storage battery casings as fuel and of inhaling the lead-laden fumes have been reported.

The metabolism of lead is quite similar to that of calcium. It is probably transported in the blood stream in the form of colloidal lead phosphate and is deposited in the bone tissue as tertiary lead phosphate. As long as the lead remains stored in the bony structures, it is essentially nontoxic and inert, but in high concentration in the blood stream, in the colloidal form, it is capable of the many toxic manifestations that are

grouped under the general term of "lead poisoning." Unfortunately any changes in the hydrogen ion concentration such as we find accompanying acute infection, especially with acidosis, may withdraw the inert tertiary lead phosphate from its reservoir in the bones and transform it into the highly toxic colloidal form, and an acute exacerbation of symptoms follows, occasionally months after the last ingestion of lead.

Lead is gradually excreted through the gastrointestinal tract and the kidneys. Any medication or pathologic condition causing acidosis will elevate the levels of circulating lead phosphate, accelerating excretion, but also increasing the possibility of acute symptoms. In infants and children, in particular, acute encephalitis may be precipitated.

Encephalitis due to lead is unfortunately one of the most frequent manifestations of plumbism in the younger age group. The symptoms are largely those of increased intracranial pressure: headache, projectile vomiting, stiff neck, Kernig sign, convulsions, transient palsies, coma, and death. On examination the spinal fluid is usually under markedly increased pressure and contains from 10 to 200 cells, largely lymphocytes, with a trace of globulin, and a normal sugar content. The mortality, even under treatment, is high, and necropsy shows marked cerebral edema and encephalitis.

Anemia in chronic cases is often marked. Aub and his coworkers[7] state that contact with lead causes the circulating red cells to become contracted, brittle, and more easily destroyed. This accelerated peripheral destruction evokes the appearance in the blood stream of numerous young erythrocytes, which are acted upon by lead with the resultant coagulation of their basophilic material which we call "stippling."

Colic is an infrequent symptom of lead poisoning in children. Constipation, however, is extremely common and may be the first complaint that brings the child to the attention of the clinician. Although it is not clearly understood, there may be a connection between sluggish intestinal function and colic, as Aub[7] reports that marked constipation is often noted during the few days preceding a typical attack of colic in the adult. Lack of appetite, nausea, vomiting, and occasionally diarrhea are other enteric symptoms.

Lead line in the gums is infrequently seen in childhood, as gingivitis is considered necessary for the formation of the lead sulphide granules which give the characteristic bluish purple discoloration of the gum margins.

Peripheral neuritis is not a frequent pediatric finding in plumbism, although transient palsies accompanying encephalitis are fairly common. In children, as contrasted with adults, foot-drop is more common than wrist-drop, and this is probably due to the greater muscular fatigue in the lower extremities of the active child. Aub discusses the

literature on this point and quotes several instances in which file cutters have developed their most severe palsy in their left hands which are subject to the greatest fatigue. His experimental work with "leaded" cats also indicates that fatigue plays a major part in causing a *locus resistentiae minoris*. Aub feels that the primary lesion is in the muscle, but most observers believe that the peripheral nerve is principally affected by lead.

As has been previously pointed out, the literature indicates that lead neuritis is solely a motor phenomenon. Goodwin's recent report[14] is a notable exception, however, since his three-and-one-half-year-old patient exhibited complete anesthesia of the trunk and extremities. The case reported by us also had a definite, though less marked, anesthesia of the involved extremities.

Recovery from lead neuritis, unless interrupted by the onset of encephalitis or by exposure to additional lead, is usually slow but complete. The first muscle groups to be affected are usually the most severely impaired and are the last to regain normal function. In adults, however, instances have been reported in which the paralysis was so widespread that death eventually resulted from impairment of the diaphragm.

Hyslop and Kraus[17] have reviewed the many theories as to the exact location of the lesion in this syndrome and conclude that the whole nerve cell is probably affected from the beginning: they call the disease essentially a "lead neuronitis." This theory is borne out by Goodwin,[14] who found myelin degeneration of the peripheral nerves, both with the Weigert myelin sheath stain and scharlach R. This degeneration was most marked in the nerves of the leg where weakness was first noted. As has been mentioned, no changes were found in the medulla, spinal cord, anterior or posterior roots, or spinal ganglia, and the muscle fibers showed only a slight possible atrophy.

The diagnosis of lead poisoning is suggested by story of pica and is most easily confirmed by the finding of the characteristic broad line of increased density at the ends of the long bones by roentgenologic examination. Much less often in children do we find the lead line of the gums and basophilic stippling of the red blood cells. Urinalyses for lead are confirmatory but time-consuming and difficult; stool analyses may indicate only ingestion without absorption. Shipley and his coworkers[18] in 1932 have given us another valuable diagnostic aid by demonstrating that lead-laden blood and tissues give a characteristic spectrographic picture.

Peripheral neuritis is suggested by gradually increasing motor weakness of the extremities, diminished or absent tendon reflexes in the involved areas, and completely negative results on electrical stimulation

over the most severely affected peripheral nerves, with "wormlike contractions" of the muscle groups innervated by nerves showing less involvement. In the case of the active child, foot-drop is the first and most pronounced evidence of neuritis, followed by wrist-drop, although generalized neuritis and paralysis is possible, with death occurring from failure of the phrenic nerve and diaphragmatic action. Diminution in sensation also occurs, although uncommonly as compared with motor involvement. Atrophy of involved muscle groups is not rare, with the thenar eminences quite often affected. When the syndrome of peripheral neuritis as described is seen in conjunction with the diagnostic evidences of plumbism, we are justified in making a diagnosis of lead neuritis.

The first essential of treatment is removal of the child from his source of lead, as complete recovery from moderate neuritis will usually take place without any specific therapy if no further poisoning occurs. Second, measures should be taken to transfer the lead phosphate in its toxic colloidal form from the blood stream to the storehouse in the bones, where it is inert and incapable of causing symptoms. Vitamin D in large doses and dicalcium phosphate will accomplish this purpose since the latter will elevate the blood levels of calcium and accelerate the deposition of both calcium and lead phosphate in the bones, with vitamin D as the catalyzing agent. Most observers now feel that it is not wise to attempt "de-leading," as originally advocated by Aub,[7] in children, since the danger of precipitating an acute encephalitis is too great. The safest procedure is to remove the circulating lead as quickly as possible from the blood stream and to allow it to be slowly excreted, via blood, kidneys, and intestine, over a long period of time in a concentration too low to cause acute symptoms.

The treatment of lead neuritis per se is largely supportive. If foot- or wrist-drop is marked, supportive casts should be worn to prevent contraction and permanent deformity. Physiotherapy is indicated, and electrotherapy, judiciously applied, may be of value. In our case, marked improvement followed within one week after the administration of a high liver and vitamin B regime, and it is interesting to speculate whether this particular form of therapy, especially the B fraction, was of value, since the relationship of the vitamin to certain forms of neuritis is well recognized.

SUMMARY

A case of peripheral neuritis due to lead in a three-year-old white girl is described. There was marked foot-drop and wrist-drop, with atrophy of the thenar eminences and diminution of sensation over the involved extremities. The literature of lead neuritis is reviewed and a discussion of the syndrome is given.

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NONHEMOLYTIC STREPTOCOCCUS MENINGITIS

Report of a Case

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THE proper diagnosis, prognosis, and perhaps, eventually, the treatment of cases of cerebrospinal meningitis caused by organisms which rarely invade the subarachnoid space can be based only on a considerable series of cases. Sufficient cases may not occur in the experience of a single observer or even in that of a large clinic. It is felt, therefore, that it is justifiable to report an isolated case of acute purulent meningitis in which the causative organism was a minute, gram-negative nonhemolytic streptococcus.

Among the last 275 cases of cerebrospinal meningitis admitted to the Infants' and the Children's Hospitals no instance of meningitis due to this organism had previously occurred. Search of the available literature was carried back to 1919 at which date Smith and Brown[1] published their classification of streptococci. Two reports were found of cases of cerebrospinal meningitis in which the organism was described as a nonhemolytic streptococcus. One was that of Rothschild[2] in which the patient was a twenty-nine-year-old male who ran an extremely chronic course with ultimate recovery. From the cerebrospinal fluid a "low-grade, pleomorphic streptococcus of the nonhemolytic type" was isolated on four occasions. No further description of the organism was given. An abscess of a tooth was postulated as the source of the infection. The second report was that of Gleich.[3] A two-month-old colored male infant had a typical onset of acute meningitis followed by block in the circulation of cerebrospinal fluid, hydrocephalus, and death from bronchopneumonia after five months in the hospital. The organisms occasionally isolated from the cerebrospinal fluid were "nonhemolytic streptococci" which were "nonbile soluble, nonencapsulated, and did not hemolyze blood. They formed chains of three or four and occasionally appeared as gram-positive diplococci." In neither of these cases was the organism defined with sufficient clarity to admit its similarity to the infecting agent of the case here reported.

CASE REPORT

F. P. (C. H. No. 202,513), white, American-born girl, aged nine years and five months, was admitted to the Medical Service May 27, 1936, with pain and stiffness of the neck of three days' duration. The family history was irrelevant. Of two siblings one had died of pneumonia at the age of five months, the other of probable congenital heart disease at the age of eighteen months.

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There was nothing abnormal in the child's dietary or developmental history, save for a long-standing disinclination to eat large meals. She had always been good-natured, active, and of at least average intelligence. She was said to have had scarlet fever at the age of six months, chickenpox at about two years, pertussis at about four years, and measles at some forgotten date.

As long as could be remembered, the child had had blueness of the lips and fingertips, which varied in degree from time to time. Although neither dyspnea, orthopnea, edema, nor cough was noticed, her activities were moderately restricted. Three years before admission here a diagnosis of congenital heart disease was made at another hospital. Over nearly the same interval of time she had had attacks of muscular pain in the legs and back, occurring at intervals of two or three months, lasting about a week, and sometimes accompanied by an upper respiratory infection. At other times these attacks seemed to be brought on by overexertion. There were no true joint pains. The last attack occurred one month before entry.

Two weeks before admission the patient came home from school with fever, sore throat, and pain in her back. There was also a rash consisting of a uniform, smooth flush without petechiae and without desquamation. The family physician suggested scarlet fever, but all the manifestations cleared up in twenty-four hours and he dismissed the possibility. The patient soon felt perfectly well but, in view of her cardiac condition, was kept in bed.

Three days before entry there was an abrupt onset of headache, most marked at the vertex, severe pain in the back of her neck, and vomiting. The headache lasted only an hour or two, but the pain in the neck persisted without relief, and on the following day the physician noticed that the head was retracted and that the child would not touch her chin to her chest. Nonprojectile vomiting continued, but she managed to retain a little orange juice and milk. There were no chills, no pains in the back, abdomen or extremities, no spots on the skin. The child was active, alert, restless, and sleepless until the night before entry when she became drowsy, mentally confused, and had a few visual hallucinations.

Physical examination showed a poorly developed and nourished child of nine and one-half years, lying in bed in a restless stupor. She was able to ask for water but would not answer questions or obey requests. Her head was markedly retracted. Her arms and legs were flexed and the legs were held in scissors position.

The temperature was 104.6° F., the pulse was 120 per minute, the respirations were 28 per minute. The skin was warm and dry without rash, eruptions, or petechiae. There were chains of small, soft cervical glands starting bilaterally at the angles of the jaw and running down the anterior borders of the sternomastoid muscles.

The head was symmetrical, and the hair and the scalp were normal. No tenderness could be elicited over the air sinuses of the skull. The eyes were tightly closed and resisted opening. The sclerae and conjunctivae were clear. The pupils were round, regular, and equal and measured 4 mm. in diameter. They reacted to light. There was no strabismus. The eardrums were intact and lustrous. There was a slight nasal discharge. The mouth was held open. The lips were of normal color but were dry and cracked. The teeth were in fair condition. The tongue was dry and coated. The tonsils were moderately enlarged and both they and the pharynx were slightly reddened. The neck was rigid and pain was elicited when anteroflexion was attempted. The chest was symmetrical. Respirations were regular and expansions were equal. Percussion showed uniform resonance. Breath sounds were normal, and there were no râles.

The cardiac apex beat was forceful and normally located. The left border of dullness was at the midclavicular line. The right border was 4 cm. to the right of the midsternal line and the supracardiac dullness was slightly increased. There was a coarse systolic thrill palpable all over the precordium but most marked at the

TABLE I

SPINAL FLUID FINDINGS

DATE	SITE	PRESSURE	APPEARANCE	GLOBULIN	SUGAR	CELL COUNT	POLYMORPHS	MONOCYTES	SMEAR	CULTURE	AMOUNT REMOVED	INTRATHECAL MEDICATION
5/27/36 5:00 A.M.	4th lumbar space	Normal	Cloudy Yellow	++++	0	14,000	98%	2%	Negative	Minute gram-plus streptococcus	20 c.c.	15 c.c. antimeningococcus
5/27/36 4:00 P.M.	3rd lumbar space	Sl. incr.	Cloudy Yellow	++++	0	11,000	98%	2%	Negative	Minute gram-plus streptococcus	30 c.c.	15 c.c. antimeningococcus
5/28/36 11:00 A.M.	4th lumbar space	Sl. incr.	Cloudy Yellow	++++	0	11,500	98%	2%	Negative	Minute gram-plus streptococcus	35 c.c.	15 c.c. antimeningococcus
5/29/36 5:00 P.M.	4th lumbar space	300	Cloudy Yellow	++++	0	13,000	96%	4%	Rare gram-plus cocci	Minute gram-plus streptococcus	45 c.c.	None
5/30/36 6:00 P.M.	4th lumbar space	Sl. incr.	Cloudy Yellow	++++	0	12,000	98%	2%	Rare gram-plus cocci	Minute gram-plus streptococcus	35 c.c.	None
5/31/36 3:00 P.M.	4th lumbar space	Sl. incr.	Cloudy Yellow	++++	0	12,000	94%	6%	Many cocci	Minute gram-plus streptococcus	20 c.c.	None
6/ 1/36 11:00 A.M.	4th lumbar space	Normal	Pus in last tube	++++	0	15,000	92%	8%	Many cocci	Minute gram-plus streptococcus	35 c.c.	5 c.c. merthiolate 1:1000
6/ 2/36 4:00 P.M.	4th lumbar space	Normal	Bloody, cloudy, purulent flakes	++++	0	11,000	94.8%	6%	Many intracellular gram-plus cocci	Minute gram-plus streptococcus	35 c.c.	

apex. The heart sounds were loud and clear. There was a loud rough systolic murmur heard over the entire chest anteriorly and posteriorly, but loudest along the left border of the sternum from the third to the fifth interspaces. The rhythm was regular.

The abdomen was without rigidity, tenderness, or spasm. No organs were felt. The external genitals were not abnormal.

The spine was somewhat rigid. The arms and legs were flexed and spastic and showed infrequent purposeless movements. There was slight clubbing of the fingers and toes, but no cyanosis.

Kernig's and Brudzinski's signs were positive. The Babinski sign was positive bilaterally. Knee jerks were weak, and ankle, biceps, and triceps jerks were not obtained. A poorly sustained ankle clonus was present.

Laboratory data showed urine which was negative save for a trace of albumin. The hemoglobin was 100 per cent (Sahli). There were 5,800,000 red blood cells and 27,400 white blood cells per cubic millimeter. The differential count (100 cells) was polymorphonuclear leucocytes 67 per cent, lymphocytes 24 per cent, monocytes 8 per cent, blasts 1 per cent. The Mantoux test, using 0.01 mg. of O.T., was negative as was the blood Hinton test. Culture of the blood taken the day of entry showed no growth after seven days' incubation under aerobic conditions at 37° C. On the third day a second culture of the blood was made. After four days' incubation under anaerobic conditions at 37° C., a small, unidentified, gram-positive bacillus grew, which was considered to be a contamination. Eight successive daily lumbar punctures yielded a minute gram-positive nonhemolytic streptococcus whose characteristics are described below in detail. Table I gives a summary of the characteristics of the spinal fluid.

The temperature ranged between 104.6° and 105° F. throughout most of her stay; the pulse, between 130 and 160 per minute; respirations, between 30 and 40 per minute. On the night of admission, in view of a purulent cerebrospinal fluid in which no organisms were found on direct smear, she was given 15 c.c. of antimeningococcus serum. On the third day, when the organism had been identified, serum therapy was discontinued. However, lumbar punctures were performed daily, and each time as much cerebrospinal fluid as possible was removed. On the sixth day she was given an intrathecal injection of 5 c.c. of a 1:10,000 dilution of merthiolate. She developed a parkinsonian tremor. The cerebrospinal fluid became thicker each day. Her condition became steadily worse and on the eighth hospital day, after a terminal temperature rise to 106° F., the respirations suddenly ceased.

BACTERIOLOGY

The organism which was consistently grown in pure culture from the lumbar spinal fluid was a minute streptococcus, the diameter of the individual cocci being about 0.1 μ. It was not decolorized by Gram's method. The organisms were so small that they may well have been missed in the direct smears from the first three spinal fluids. Once recognized, they were identified in all subsequent direct smears and in the last spinal fluid were found within the cytoplasm of the neutrophiles as well as extracellularly.

Attempts were made to grow the first generation from the spinal fluid under aerobic and under anaerobic conditions and at 10 per cent carbon dioxide tension on chocolate agar slants; under the same conditions on blood agar plates, peptone blood agar plates, and in 50 per cent horse serum broth, and dextrose meat infusion broth. Of these the only

growth was obtained under 10 per cent carbon dioxide tension on chocolate agar. After twenty-four to forty-eight hours this medium showed minute, pinpoint, shiny, gray colonies. After the third generation the organism grew readily on all the aerobic media. On the blood plates it produced pinpoint gray colonies which, even after several subcultures on plain and peptone blood agar, failed to show the slightest hemolysis, either clear or greenish. In the fluid media it grew as tiny white balls of sediment, leaving the broth itself clear. Smears of these showed the same minute cocci in very long chains.

Growth from the blood plates was taken up in saline and injected intraperitoneally into mice in 0.25 c.c. and 1.0 c.c. doses without apparent effect upon the animals.

No immunologic studies were made.

Pathology.—(A-36-87.) Postmortem examination was begun three and one-half hours after death. The anatomic diagnoses were: acute purulent meningitis of brain and cord (Gamma streptococcus), ventriculitis, dilatation of ventricles, choroiditis, congenital heart disease (dextroposition of the aorta, interventricular septal defect, pulmonary stenosis, right ventricular hypertrophy), anomalous left vertebral artery, clubbing of fingers and toes, acute otitis media (left, *Streptococcus viridans*), bronchopneumonia. As the significant findings were in the heart and central nervous system, the pathologic descriptions will be limited to these systems.

Heart.—The heart presented a rather typical tetrallogy of Fallot. The organ was moderately enlarged. All the pericardial surfaces were smooth and glistening. The right auricle was slightly hypertrophied. There was a patent foramen ovale measuring 12 mm. in diameter. The tricuspid valve was normal, measuring 72 mm. in circumference. The right ventricle was definitely hypertrophied, its wall measuring 10 mm. in thickness. The papillary muscles were not abnormal. There was an interventricular defect 12 mm. in diameter through which bulged the base of the right segment of the aortic valve. The pulmonary valve measured 20 mm. in circumference and had two segments. The left auricle and the mitral valve were normal. The valve measured 38 mm. in circumference. The left ventricle was reduced in size. Its wall was 10 mm. in thickness. The aortic valve had three segments and measured 40 mm. in circumference. A portion of its lumen straddled the interventricular septal defect. The endocardial surfaces of all the chambers of the heart were smooth and unbroken and were without evidence of vegetations. The coronary arteries were normal in their origins and distributions. Microscopically the heart was not abnormal.

Brain and Cord.—The brain weighed 1,286 gm. (normal weight 1,275 gm.). There were no abnormalities in the skull. The dura was not thickened nor was it anywhere adherent to the arachnoid layer. Over the entire surface of the brain the subarachnoid space contained a moderate amount of turbid, light yellow gray fluid. Over the hemispheres the exudate was moderate in amount and seropurulent in character. Around the base of the brain it was larger in amount, more plastic in character, and covered the greater part of the optic chiasm and the roots of the cranial nerves.

The entire ventricular system was moderately dilated. Posterior to the basal ganglia the right lateral ventricle was more dilated than the left and was filled with a green yellow purulent exudate. The temporal horn of the right ventricle was more dilated than that of the left. Anterior to the foramina of Monro the left lateral ventricle was more dilated than the right and was filled with the same green yellow

exudate (Fig. 1). The third and fourth ventricles were moderately dilated and contained considerable exudate. The foramina of Monro and the aqueduct of Sylvius were patent to probing but were partially closed off by the exudate. The foramina of Luschka were not involved. All the ependymal surfaces were covered

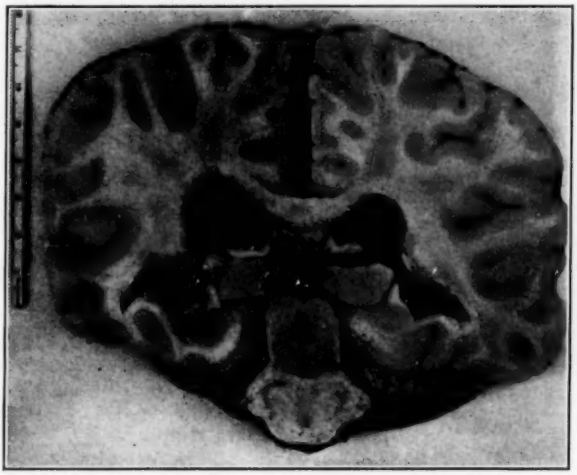

Fig. 1.—Transverse section of brain at level of pons, showing meningitis, ventriculitis, and dilatation of ventricles.

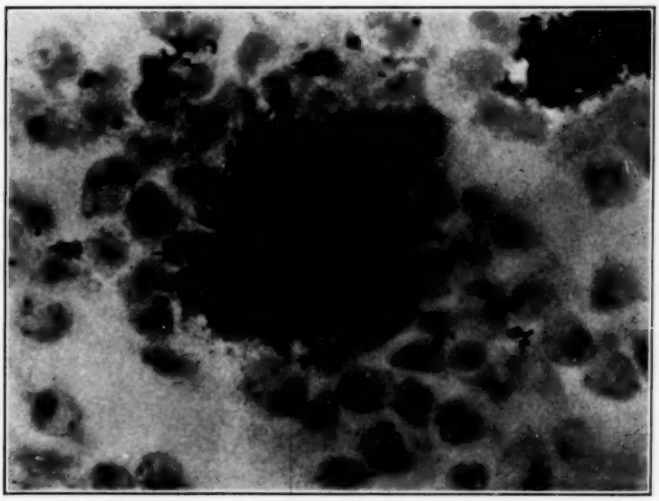

Fig. 2.—Photomicrograph (×1300) showing clumps of minute streptococci in ventricular exudate. Probably in part postmortem growth. Arrows point to well-defined chains.

by varying degrees of exudate. The choroid plexuses were similarly covered. The cord was edematous and its subarachnoid space contained much of the thick greenish-yellow exudate.

The dural sinuses were not abnormal. The cranial bones showed no fracture or inflammatory process. The right middle ear was free of exudate. The left middle ear was filled with a thick, light yellow, fibrinopurulent exudate from which *Streptococcus viridans* was grown in pure culture. The mastoid cells on this side were sclerotic but contained no purulent material.

Microscopically there was a subarachnoid inflammatory process that varied in intensity from area to area, being most marked around the base of the brain and around the spinal cord. In the subarachnoid space there were large masses of degenerating fibrin and granular débris through which were scattered numerous neutrophiles, lymphocytes and large mononuclear cells. There was considerable fibroblastic proliferation around the vessels and in the pia. Between the fibroblasts were many inflammatory cells. There were rare extravasated red cells and here and there were small clumps of the minute, chained coccus (Fig. 2). The meningeal vessels were moderately distended. A very similar process was present over the ependymal surfaces, although here the proliferative response was not so marked. In places the ependyma was broken and there was extension of the inflammatory process for a short distance into the nervous tissue.

SUMMARY

This case of acute purulent meningitis was unusual in that the infecting organism was a minute, nonhemolytic streptococcus.

It is at once suggested that the meningitis might have originated from a septic embolus thrown off from a thrombus superimposed on the congenital heart disease. Careful microscopic and macroscopic search of the endocardium failed to show thrombus, vegetation, or scar. Spread of infection from the left middle ear is another possible explanation. Otitis media was not noted before death, and at postmortem the process was acute and apparently recent. The left mastoid cells were not actively involved. There was no evidence of spread through the dura. There remains the possibility of a blood stream invasion from some other source. The febrile attack with sore throat, back pain, and rash, and occurring eleven days before the onset of the acute symptoms would fit with this last conception.

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Critical Review

ACTIVE AND PASSIVE IMMUNITY

Oral Vaccination Against Colds

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I

Topley[1] states that colds are not clinical entities and that they defy definition on clinical grounds. Disputes may even arise as to what portion of the upper respiratory tract is involved in these conditions.

The exact etiology of colds is also unknown. None of the offending organisms usually mentioned as being associated with colds have ever been shown to be causative factors. Such organisms as have been described as etiologic agents may be found in the upper respiratory passages of normal individuals. Even though they may not cause experimental "colds" or initiate the human disease, such organisms may cause infections and produce purulent discharges.

Dochez and his collaborators[2] among others present evidence to show that the common cold is caused by a virus. In the light of this work, organisms found in the upper respiratory tract would be either secondary invaders and potentially dangerous or chance inhabitants activated into a virulent state by some unknown factor. If this work is confirmed, the individual with a "cold" may have the acute or first phase of the disease produced by a virus or some unknown factor, and a later phase caused by secondary organisms. The only reason for vaccinating against colds then would be based on the presumption that the use of a vaccine would shorten this secondary phase or perhaps prevent its occurrence.

For years, either stock or autogenous vaccines have been used to abort, to lessen the severity, or to decrease the number of colds in susceptible individuals. They have been used with indifferent and inconclusive results.

Wallfield[3] gives a very comprehensive review of the subject and states that experimental vaccination against colds does not give decisive results. In his vaccinated group, he obtained a decrease in the severity of the infection as measured by the number of days of temperature over 100° F., but only a slight reduction in the actual number of infections. Brown[4] did not have many cases in his groups, but such subjects as he had were thoroughly studied. He took into consideration age, sex, race, height, fatigue, previous history, environment, sleeping quarters, clothing, and diets. His statistical results show little if any improvement as regards common colds in the experimental group as a whole compared with the control group, although some individuals in the experimental group appeared to have received some benefit. He thought that better results might be obtained by increasing the dose of antigen administered or by employing the particular antigen to which the vaccinated individual was susceptible.

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Ferguson, Davey, and Topley[5] observed 138 inoculated persons and 148 uninoculated controls from November to May. Seventy-eight and three-tenths per cent of the inoculated and 70.3 per cent of the uninoculated contracted colds.

Jordan and Sharp[6] wrote that vaccinated individuals are "quite likely inclined to notice and report colds more carefully" (as compared to the unvaccinated). Rhinitis and bronchitis developed about equal in frequency in their vaccinated and unvaccinated groups. In the vaccinated group "most of them optimistically declared that they had received definite benefit in protection against colds." They state that "satisfied patient" conclusions differ widely from those of "controlled statistics."

Although the treatment of the common cold by mixed vaccines obtained from the respiratory tract has many adherents, Gay[7] believes that whatever success is obtained must in the absence of any proved etiologic agent in this disease be attributed to a nonspecific form of protein stimulation.

II

Some preliminary work on oral vaccination must be reviewed. Besredka[8] was able to vaccinate orally animals and man against dysentery, typhoid fever, and paratyphoid fever. He concluded that the titer of bactericidal properties, complement fixation or other antibodies was no proof of immunity. The advocates of oral vaccination, however, feel that the antibodies or substances formed after vaccination per os are a measure of resistance. Although Besredka vaccinated per os, to my knowledge he never proved that oral vaccination with gastrointestinal organisms was as good as, not to say, better than parenteral vaccination with the same organisms. He did demonstrate, however, that oral vaccination by dysentery organisms was not associated with reactions so severe as those which followed parenteral injections.

People may be vaccinated against typhoid fever, dysentery, and paratyphoid fever per os. These are gastrointestinal diseases, and, since the portal of entry of the bacteria is through the intestine, theoretically protection might be logically expected to be established there. But are antibodies produced better here after ingestion than by parenteral injection? Can oral vaccination protect better than parenteral vaccination against any organism which has its portal of entry elsewhere than in the gastrointestinal tract? However, it is obvious that vaccination per os is more convenient and is less likely to be associated with or followed by untoward reactions.

If it is admitted that antibodies may be as good, if not better when produced by parenteral than by oral vaccination, and if we know that the value of parenteral injections in warding off colds is dubious at best, then fairly conclusive evidence would have to be presented before one could accept the fact that ingested vaccines are better able to prevent colds than the now nearly discarded parenteral injections.

Howell[9] states that Ramon and Zoeller have shown that oral immunization to diphtheria and tetanus was less successful than other methods of immunization against these diseases.

Cooper,[10] on the other hand, reported successful immunization against pneumococcus type I in rabbits by introducing the type I vaccine into

the buccal mucous membrane. Jones[11] stated that intrabronchial inoculation into rabbits gave no better protection than intraperitoneal injections.

Ross[12] showed that rats were promptly immunized by ingestion of type I pneumococcus. This protection lasted from five days to four months after the last ingestion of vaccine. Thus, it was demonstrated that one could vaccinate rats orally against respiratory infections. His rats developed protective antibodies, the concentration of which in the blood serum resembled that found in human beings convalescing from pneumonia. The results with type II pneumococcus were not so definite as those obtained with types I and III. Much trouble was experienced by this worker due to the fact that many of his young rats had a high degree of natural resistance to type II pneumococcus; yet the general results indicated that the blood acquired protective powers when the animals were fed vaccine. He likewise immunized human beings by having them ingest pneumococci. Seventy-five per cent of the individuals tested formed protective antibodies against type I, and 60 per cent against type II with approximately the same results for type III as for type II. He did not find the concentration of antibodies high, but he states that the quantities are of the same order of magnitude as are found during recovery from pneumonia. These protective substances appear promptly, being present within two to three days (following six feedings) and were found in most serums examined from seven to fourteen months after vaccination. Ross believes that the protective substances described indicated immunity to pneumococcus, and also believes that the appearances of these substances in the blood of pneumonia patients at the time of their recovery give further support to his contention. Agglutinins were not detected by this author in the serums in which protective antibodies were found.

Kolmer and Rule[13] fed rabbits vaccine. The animals thus fed did not succumb to pneumococcus pneumonia and septicemia when the organism was subsequently introduced intratracheally.

Kolmer and Amano[14] gave rabbits type I pneumococcus orally and were able to protect occasionally against fatal pneumococcus septicemia and meningitis.

Powell, Jamieson, Bailey, and Hyde[15] suggested that a pure antibody might be enhanced in effectiveness by the addition of heterophile antibody. They thought that, since the tissue of horses contains heterophile antigens and their serum does not contain heterophile antibody, the serum antibody obtained from horses could be enhanced in its curative qualities by adding heterophile antibody obtained elsewhere, as from the rabbit or cow, whose tissues contain no heterophile antigen. They adopted a different method of estimation of the effect of pneumococcus than that of the well-known mouse test since in their opinion this test was one for determining prevention and not cure. They stated that the mouse would be useless in evaluating the antipneumococcal action of heterophile antibodies since tissue of this animal contained heterophile antigens. No animal of like type in which there is heterophile antigen in the tissue (guinea pigs, mice, and dogs) should be used. Both human beings and rabbits are alike biologically in their lack of heterophile antigen. Therefore, rabbits were used experimentally. These were injected intradermally and twenty-four hours later were given intra-

venous amounts of various antibodies, pure heterophile antibody, horse antipneumococcus serum, mixed antibody containing horse antipneumococcus serum, and heterophile antibody. The usual mouse protective antibody seemed to be made more effective when fortified with heterophile antibody. In this experiment the experimental doses were given intradermally. The number of animals used in experiments with type I pneumococcus seemed to me to be too few to warrant definite conclusions. Although a few more animals were used in experiments with type II organisms, the results obtained seemed more clear-cut, and heterophile antibody seemed to aid in protecting. Both heterophile antibody serum and specific antibody seemed to protect against type III pneumococcus. Heterophile antibodies are thus suggested as protecting against infection.

III

What are heterophile antibodies? When emulsions of guinea pig organs are injected into rabbits, antibodies other than specific ones may be produced. Thus an injected antigen may produce antibodies which will react with other antigens totally unrelated to the one injected. Such nonspecifically produced antibodies are termed heterogenetic or heterophile antibodies, and the antigen producing them is called heterophilic or heterogenetic antigens, or Forssman antibodies or antigens, after the worker who first described them in 1911.

Heterophile units are ascertained by testing to what titer serums have the ability to lyze washed sheep red blood cells.

Wells[16] calls these antigens a striking example of the existence of identical antigenetic properties in materials of apparently unrelated biologic origin. Bull[17] states that these antigens are thermostabile. Organ plasma contains the antigen. It is a complex which can be disrupted by treatment with alcohol. Human tissues may contain heterophile antibody. Sherwood[18] points out that heterophile antigen is retained by the tissues and withstands boiling for one hour. Its presence may intensify or perhaps be responsible for some cases of serum intoxications. To Landsteiner and Levine[19] "it appears that the capacity of hemolyzing sheep blood is a property of a large number of otherwise different antibodies, and the corresponding so-called Forssman antigens are not identical, but have some sort of similarity." It is a much more "natural assumption that sheep blood contains one or perhaps several Forssman substances possessing the property of reacting with various antibodies."

Should the serum of animals immunized with a heterophile antigen be injected later intravenously into another animal whose organs contain heterophile antigen, a severe reaction may result. This happens possibly through the reaction between the antigen present in the tissues and the antibodies present in the serum of the immunized animal. Heterophile antibodies present in serum may be absorbed by heterophile antigen-containing organs. Heterophile antigens are termed haptens (partial antigens) and are usually lipoid or carbohydrate fractions, although it has been stated to be a combination of both.[20] Topley[1] states that the organs of guinea pigs, horses, dogs, cats, mice, fowl, and tortoise stimulate the production of heterophile antibodies when injected into the rabbit. On the other hand, organs of man, rabbit, sheep, ox, rat, goose, pigeon, eel, and frog do not. In general, those animals which contain heterophile antigens in their tissues do not have

it in their red blood corpuscles. (Domestic fowl has it in both blood and other tissues.[17]) The hemolysin produced by the rabbit in response to an injection of guinea pig kidney is not identical with that produced in response to an injection of sheep red cells. The hemolytic serum in the latter instance contained a mixture of hemolysins, only one of which corresponded to the heterophile antigen; the serum prepared by immunization with guinea pig kidney appeared to contain the heterophile antibody alone. Topley states that in assessing the significance of all such experiments on antigenetic constituents and Forssman's heterophile antigens, one must remember that "antisheep hemolysin is a normal constituent of rabbit serum, although it occurs only in low titer."

It is probable that the reason antigens of organs of bacteria may cause similar reactions is that they contain similar, as well as their own specific, substances. Probably no antigen is ever in a pure state so that there is always the possibility of a combination response from any injected antigen.

All the findings on heterophile antigens and antibodies would be of no moment, and such evidence could be discarded as irrelevant were it not for the fact that certain workers have tried to link their presence to immunity. Bailey and Shorb[21] felt that a large amount of heterophile antibody present implied a greater resistance to a primary pneumococcus invasion and was a deterrent to the growth of this organism after it had been introduced. They demonstrated that various pneumococci and one culture of streptococcus produced heterophile antibodies characteristically the same as those antibodies produced by the injection of boiled sheep red blood corpuscles. This hemolytic antibody was removed by hemologous or heterologous boiled pneumococci or boiled sheep corpuscles. Injections were made intravenously with some control injections given intraperitoneally and the heterophile antigen component sometimes was as high as 10,000 heterophile units (pneumococcus type I). On the whole, other pneumococci types did not produce so high a titer of serum. The best results were obtained with Pr. I., probably a smooth, and D. R. I., a rough strain of pneumococci type I. Rabbits were then injected intravenously and intranasally and fed organisms (type I pneumococci). Killed organisms were given intravenously and by mouth, living organisms intranasally and a less virulent one in some instances intravenously. The highest production of hemolysin in rabbit serums follows the intravenous injection (5,000 to 10,000 units), but heterophile antibodies were also formed by oral ingestion (2.5 to 166 units), though to a lesser degree. They tried to protect rabbits by injecting only sheep red blood cells (nonspecific heterophile antigen) against type I pneumococcus, but the authors felt that a "sufficient number of experiments under varying conditions had not been done thus far to justify drawing definite conclusions as to the protective properties of antisheep hemolytic serum in pneumococcus infections with the different types of this organism, although the results obtained with type I pneumococcus demonstrated considerable protection in rabbits when infected with this organism."

Bailey and Shorb[22] did further work on the thesis that the heterophile antigenic fraction of pneumococci may have definite biologic significance in pneumococcus immunity. Curiously, in this work, they found that pneumococci were more or less able to absorb hemolysin from different

types of serums. One organism, D. R. I., absorbed as much of the Shiga hemolysin as any of the heterologous Shiga antigens, demonstrating the polyvalency of the heterophile antigen. Incidentally, they deduced that there is no definite relationship between roughness and smoothness and the ability to stimulate the production of heterophile antibodies in the rabbit. They did more protective experiments in rabbits. They immunized them with heterophile and nonheterophile antigens and then infected them with pneumococci. Relative protection was claimed to be more striking when the infecting organism was a stock strain grown on rabbit blood beef infusion in decided contrast to the lesser degree of protection and the higher mortality rate in rabbits when the same organism had been used, but whose virulence had been enhanced by two passages through rabbits. Even here, however, there was some slight protection. Naturally there was a great deal of interest shown as to what would produce heterophile antibodies, and it was soon demonstrated that heterophile antigens were not only present in organs, but also in the fractions of organisms. Powell[23] reported on the presence or absence of heterophile antigens in certain bacteria. Such substances have been found in pneumococci, *H. influenza, Micrococcus catarrhalis,* lipoidal substances, and carbohydrate fractions. Shorb and Bailey[24] stated that heterophile antigen may be the result of a certain environment or of particular metabolic processes since many bacteria of the respiratory and intestinal tracts of man and animals contain it. It may also be a generic or family characteristic. It is an integral part of the cells. They investigated 187 strains of bacteria representing 81 distinct species, 29 genera, and many more found to contain this antigen.

Iijima[25] has demonstrated that the Forssman antibody (Shiga bacillus) contained in antishiga immune serum derived from the rabbit is independent of the specific agglutinin, since absorption of the Forssman antibody by goat's red corpuscles leaves the agglutinin content of the serum unaltered.

Rockwell and Van Kirk[26] compiled their results as to the heterophile activity of various bacteria and plants. They found that many bacteria including *B. mucosus,* meningococci, *H. pertussis,* as well as such foods as spinach, beets, and turnips contain heterophile antigen. Several strains of *B. abortus,* gonococcus, and *B. acnei,* as well as asparagus, green beans, peas, rhubarb, and celery, did not contain any heterophile antigen. Turnips, beets, and spinach produce heterophile antigens. The authors found that old isolated cultures of *H. influenza* did not produce any heterophile antibody and that rough strains of *H. influenza* and in one instance of *B. mucosus-capsulatus* were relatively free from antigen.

Powell[27] treated rabbits orally with various heterophile antigens and indicated that heterophile antigens passed through the intestinal tract and incited production of antibodies.

IV

Powell started to immunize by oral vaccination in 1926. Most of the subsequent work in oral vaccination against colds has been done by Rockwell, Van Kirk, and Powell. In 1935, these authors[28] reported a series of 500 patients who had received vaccine enterally with 536 controls. The vaccinated individuals had received 100 billion pneumococci (rough strain, D. R. I., Neufeld type I) and 100 billion strepto-

cocci (virulent mouse strain, probably a smooth type). Both of these organisms produced heterophile antibodies. The treated individual took one capsule each day before breakfast for seven days and one capsule a week throughout the remainder of the winter season. The authors interpreted their data in the light of subsequent happenings to the two groups. Did the individuals thus treated have fewer colds or colds of less severity and did the patients treated have more heterophile antibodies in their blood serums as a result of their vaccination? The injected and controls were taken from various groups of society—a general group and groups of life insurance employees, nurses, medical students, and machine shop workers. They claimed that the vaccinated group had less colds. The incidence of cold attacks for the previous three-year period of the group was obtained from the individual patient's history—presumably from memory. Although such information may not be absolutely accurate, it may be argued that the fact still remains that intelligent individuals usually know whether they are better or not, and, even though there may be errors in estimation of the incidence of cold attacks, patients ought to be able to tell gross differences in well-being.

It should be said that the tendency was in the right direction—for those treated to have fewer colds. When the control groups were analyzed, there was no marked difference in the incidence of colds before and after the experimental year, although there was a decrease in the total number of colds in the group that ingested the vaccine. Thirty-eight treated individuals with a history of continuous colds were improved to the point where they had only forty-one colds and of 9 like controls only one became better. The figures of the authors were computed, and it was claimed that the treated group had a decrease of 57 per cent in the number of colds while the controls had a decrease of only 12 per cent. Rockwell and Van Kirk[29] studied 47 of these subjects for the heterophile antibody content of their serums and made that the subject of a subsequent communication. Thirty of the individuals studied had been treated by oral vaccination, and 17 served as controls. Seventeen of the 30 patients had from 60 to 600 heterophile units in the blood stream. Thirteen had less than 60 units of antibodies. The first group showed a marked decrease in the number of colds while the individuals in the second group had a slight increase. Fifty-six and six-tenths per cent of the total were benefited; the remainder were not. Since the control group had a natural decrease of 12 per cent, benefits could be claimed for only 44.6 per cent of the treated group.

Rockwell, Van Kirk, and Powell[30] report further on a series of 445 treated subjects with 469 untreated controls compiled during the winter of 1935 and 1936. The capsules ingested this time contained 25 billion pneumococci, 5 billion *H. influenza*, 15 billion of streptococci, and 5 billion *M. catarrhalis*. The reactions following the ingestion of these capsules were mild, consisting of a grippelike feeling and mild intestinal discomfort, and then only occurred occasionally. Briefly, they claimed a 70 per cent decrease in colds this year as compared with only 26.3 per cent decrease in the controls. Subjectively, 81.7 per cent stated they were greatly benefited. Forty-three of 46 persons who suffered continuous colds with constant coryza throughout the year contracted less than one cold per person that winter. The authors state that the resultant immunity is of short duration and treat-

ment must be more or less continuous throughout the year. An interesting point was the fact that the 469 controls showed a decrease of 26.3 per cent of colds. This was over twice that reported for a previous control group. It is not clear in this article why the insurance company employees had a protective differential of only 23.5 per cent as compared to 43.7 per cent for the entire group. In another report, Rockwell and Van Kirk[31] presented figures on a study of the heterophile antibody content of 80 persons for the 1934-35 season and 81 for the 1935-36 season, which together with the 30 previously reported make 191 patients in whom the heterophile content of the blood serum is reported. The conclusions are reached that of the 50 persons who developed 120 or more heterophile units per cubic centimeter, there was a reduction of 88.3 per cent in the incidence of colds, and all treated subjects were benefited. Of 36 persons developing from 60 to 100 heterophile units per cubic centimeter, there was a reduction of 63.1 per cent in the incidence of colds and 4 were not benefited. Of 105 persons who developed less than 60 heterophile units per cubic centimeter, there was a reduction of 47.4 per cent in the incidence of colds, and 47 cases were not benefited. The 51 persons who were not benefited by the vaccine developed less than 120 units of heterophile antibody, 47 less than 60 units.

V

An estimation of the efficiency of any therapeutic procedure that will aid in terminating colds or in lessening their severity is extremely difficult. It is relatively easy to determine whether diphtheria antitoxin is of value. It is another story with colds. People usually do not die because of their colds, nearly everybody gets them, some more easily than others, and some more often than others. Colds normally may vary in severity in different individuals and even in the same individual. They likewise may be aggravated by physical agents such as drafts and exposures. Many infections termed colds may be secondary infections following an irritation rather than secondary infections following a virus infection. The length of time a cold lasts is variable. There is no physician who has not noted that colds vary in severity in different members of the same family. Likewise it is known that if colds are frequent, the nose and throat should be investigated, and if they are still persistent, it is more than possible that an allergic state may account for the recurrent attacks. Usually there is something fundamentally wrong with the individual who has from eight to ten colds a year. Another thing that is obvious to practitioners is the fact that individuals who suffer from colds tend to become better as time goes on, unless there is an underlying nasal pathology. The state of the weather, the amount of humidity, and the prevalence of sunshine are all factors. People in Puerto Rico are less likely to get streptococcus infections than those who live along one of the inland river cities. The inhabitants of some cities are more prone to have upper respiratory infections because the air breathed may be laden with particles of soft coal and dust. It is obvious that difficulties arise in estimating the results of any therapeutic measure designed to have an effect on colds, either as to incidence or severity of the attacks. Since the reliability of human memory for past events is almost zero in the opinion of most statisticians. statements made by patients as to the number of colds they have had in the past must be considered with skepticism. It is clear, however,

that an individual may be struck by the absence of any colds and that this may impress him so that his evidence becomes of value. A patient may conquer his tendency to get colds and become better because of many extraneous factors such as better hygiene, self immunization, and less exposure, and these possibilities must be considered in any estimation. The reader is referred to Doull for a method of studying the clinical effects of therapeutic procedures.[32 a, b]

Does oral vaccination produce more or better heterophile antibodies than are produced after injection? If the answer is negative, we must revert to the original position that, since parenteral vaccination has not been a success, the mere presence of heterophile antibodies does not argue much for protection. On the other hand, immunization against colds is fleeting. Thus any antigen must be continuously administered to keep the immunity at a protective level. Antigens can be given per os over long periods, but parenteral injections are not well tolerated even for a few doses. It appears from the reports that no harm is done to the human being if he ingests capsules containing bacteria.

The logic on the use of oral vaccination may be summarized in the following propositions.

1. Certain organisms that accompany or produce colds in man produce heterophile antibodies in animals.
2. Such heterophile antibodies may protect animals against certain bacteria that may produce colds in man.
3. Heterophile antibodies appear in the blood serum of human beings after infections with certain organisms (actually heterophile antigens) that produce or accompany colds in man.
4. Heterophile antibodies appear in the blood serum of human beings after the ingestion of certain organisms (heterophile antigens) that produce or accompany colds in man.
5. Organisms that complicate or produce colds may be considered as heterophile antigens which can produce heterophile antibodies.
6. These organisms (specific heterophile antigens) that produce or complicate colds in man can be ingested by the human beings, and heterophile antibodies will be produced which will protect the individual against future colds or at least against the secondary infections that complicate future colds.

Propositions 1, 3, 4, and 5 might be tentatively admitted, but it would seem to me that 2 and 6 require further evidence before they can be accepted. In short, the case for oral vaccination against colds has not been made.

The recent work on this subject is important and should be repeated. It might be advisable to have an epidemiologist join in any future study so that the factors of error can be carefully analyzed for possible effects they might have on conclusions.

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Round Table Discussion on Nasal Sinus Disease

Chairman: Dr. L. W. Dean, St. Louis, Mo.
Assistants: Dr. Edward C. Mitchell, Memphis, Tenn.
Dr. John J. Shea, Memphis, Tenn.

Nasal Sinus Disease

L. W. Dean, M.D.

In treating chronic purulent nasal sinusitis, we should always bear in mind the possibility that allergic rhinitis and sinusitis are important etiologic factors in the production of the purulent process. Dr. C. S. Linton,[1] working in the Oscar Johnson Institute, proved conclusively that whenever stasis was produced in the sinus of an animal or in the nose, infection followed. He showed that, while nasal secretion when fresh has a slight bactericidal action, on standing this is lost and bacteria will grow in the nasal discharge. In allergic rhinitis we have vasomotor disturbances with swelling of the nasal mucous membrane. This edematous membrane easily blocks the opening of a nasal sinus producing stasis with resulting infection. Allergic rhinitis produces such marked edema of the nasal mucosa that it is difficult to understand why we do not always get infection of the sinuses. There is but little difference between the end-result of allergic rhinitis and the edematous rhinitis that is present in nephrosis. In nephrosis with edema of the membrane we get a blocking of the sinus ostium with infection just as we do in allergic rhinitis. The only way to keep the sinuses normal is to have good ventilation and drainage. Anything that interferes with this will produce sinus disease.

Allergic rhinitis not only produces a swelling of the mucous membrane which is present during the attacks of allergic rhinitis, but once present it leaves behind changes in the mucous membrane which increase its thickness. In the last year in only one of a great many patients who have suffered from hay fever have we seen a clinically normal membrane. This patient had only one mild attack of hay fever. With several attacks the membrane is certain to become pathologic. Patients with hay fever often suffer during the winter with recurrent upper respiratory upsets with nasal stoppage. This is due to the chronic vasomotor rhinitis which is the result of acute attacks of allergic rhinitis. A patient who has suffered from perennial allergy with nasal stoppage and sneezing and who has been completely relieved by the avoidance of allergens has, as a result, nasal chambers with good breathing space. However, the mucous membrane is paler than normal; it is thicker than normal; it is somewhat boggy. If a biopsy is performed, a typical mild chronic vasomotor rhinitis will be found present. In my judgment attacks of allergic rhinitis in infants

leave behind a thickened membrane which predisposes to the formation of polyps. Such patients throughout life present the swelling of the membrane. There is another type of case, the pure infection without allergy. In such a case the mucous membrane of the nose is thin and remains so throughout life.

We find patients with chronic vasomotor rhinitis in which on inspection we suggest the diagnosis of allergic rhinitis. There is no history of allergy in the family. There is no increase in the eosinophiles in the blood or in the nasal discharge. All skin tests are negative; the intramucosal tests are negative. If a biopsy is performed, we get the same picture of edema as in allergic rhinitis, but the increase in eosinophiles which is so characteristic of allergic rhinitis is not present. Very often such conditions can only be improved by a proper diet, the correction of endocrine dyscrasias, or both. Some such cases with proper diet month after month show a consistent shrinkage of the mucous membrane of the nose. There is no reason for saying that these patients are allergic. I know of no way of proving that at some time the individual did not suffer from acute allergic rhinitis. Rackemann, of Boston, estimates that 50 per cent of the cases of vasomotor rhinitis are nonallergic and that they do not differ in appearance from allergic rhinitis. Cameron, of Glasgow, places the figure at 40 per cent. Our percentage would be much lower. We do, however, see a number of patients with so-called nonallergic vasomotor rhinitis which we, at least, are not able to prove are in any sense allergic. Patients with nonallergic vasomotor rhinitis may develop polyps just the same as in typical allergic vasomotor rhinitis.

The treatment of chronic vasomotor rhinitis is an important thing in the management of chronic purulent nasal sinusitis if both are present. Every patient with vasomotor rhinitis should have a very thorough allergic work-up. The following is an outline of our method of studying cases of vasomotor rhinitis:

I. History
II. Examination of the ear, nose, and throat
III. Nasal smears
IV. Blood count
V. X-ray examination
VI. Bacteriologic examination
VII. Dietary deficiencies
VIII. Endocrine disturbances
IX. Skin tests
X. Intramucosal tests
XI. Passive transfer
XII. Test for bacterial allergy
XIII. Study of leucopenic index
XIV. Result of avoiding certain allergens.

The treatment of allergic rhinitis is immunologic and laryngologic. Not only should the patient avoid the substances to which he is sensitive or be desensitized if avoidance is impossible, but the nose and the nasal sinuses must be made normal. Adenoids, if present, should be removed; deflected septums should be corrected; exostoses of the septum should be eradicated. There is a vicious circle made up of allergic rhinitis and infection. Every trace of infection about the nose must be removed if we are to get a good result in the allergic rhinitis, and every trace of the allergic rhinitis must be removed if we are to get a good result in the infection; thus we must attack the two things together. We must keep in mind the fact that the first step in the treatment of the infection is to have good drainage and ventilation

[1]Linton, C. S.: Ann. Otol. Rhin. & Laryng., September, 1930.

[2]Dean, L. W.; Linton, Lloyd D., and Linton, C. S.: An Intramucosal Test for Hypersensitivity in Allergic Rhinitis, Ann. Otol. Rhin. & Laryng., June, 1935.

of the sinuses. We may be able to get this by immunologic treatment. It may be necessary to do some minor surgical work. This, however, should be avoided if possible. In this connection we must remember that there is such a thing as bacterial allergy. The term is not a good one unless we are also going to speak of ragweed allergy, etc., because the cytology and pathology of the tissues show them to be the same in bacterial allergy as they are when the allergen is ragweed or anything else. In bacterial allergic rhinitis we get similar tests using the vaccine, to those which we get using ragweed in connection with ragweed allergic rhinitis.

In making a diagnosis of allergic rhinitis, it is necessary to determine the sensitivity of the mucous membrane to various protein substances. Skin tests do not give information as to the sensitivity of the nasal mucosa. The sensitivity of the nasal mucosa can best be determined by using the intramucosal test.[2] It often happens that a patient is skin negative to a given allergen, and it is found that with the intramucosal test the mucous membrane reacts and that the patient gets complete relief by the avoidance of the allergen to which the mucous membrane of the nose has been found sensitive.

We are inclined to think that skin tests are more often likely to give information as to the past allergic history of the patient than to his present condition. Reagins may be formed during an acute allergic attack in all the tissues of the body except the cerebrospinal fluid and the aqueous humor of the eye. As soon as the attack is over, the elimination of these substances begins. They leave the circulating media of the body first and probably leave the skin last. A patient may have ragweed hay fever in August, may give positive skin test for ragweed and positive reactions on passive transfer in December, and may give only the positive skin tests in the spring.

In addition to the immunologic and laryngologic treatment of allergic rhinitis, particular attention must be given to the correction of dietary disturbances and endocrine disorders. A proper diet helps in the management of every case of allergic rhinitis. It is conceivable that by improving the nutrition the permeability of the mucous membrane to allergens may be interfered with.

Certainly trauma of the mucous membrane as a tonsillectomy, sinus operations, operations on the septum, cautery of the nose, the use of ionization, etc., all, by interfering with the protective mechanism of the mucous membrane, permit the ready entrance of allergens into the tissue of the body with resulting sensitization. Many cases of asthma appearing for the first time following these procedures have been reported.

As it is the vasomotor rhinitis which blocks the ostia of the sinus, its treatment is most important. Most patients with chronic vasomotor rhinitis get satisfactory results from immunologic treatment plus the correction of septal defects, the removal of adenoids, etc., together with proper dietary and endocrine therapy. The cases of nonallergic rhinitis in our experience have yielded only to laryngologic procedures plus proper diet and the correction of endocrine dyscrasias. The nasal procedures that are used for the correction of vasomotor rhinitis as ionization, cautery, the use of the endotherm needle, carbolic acid, trichloracetic acid, alcohol, and radium all produce a fibrosis with a splinting of the mucous membrane which interferes with its swelling.

We should say a few words about ionization which is used so much today for hay fever and perennial allergy. Ionization as used in this country for allergic rhinitis is a combination of galvanism and iontophoresis. It acts by producing a hyperplasia and a metaplasia of the epithelium and by splinting the mucous membrane of the nose. The changes in the tissue interfere with the absorption of allergens so that hay fever is benefited, first, because the ionization interferes with the penetration of the tissue by the allergen and, second, because the tunica propria is splinted and does not swell as readily as before.

Several months after its use there were found in the nose areas covered by ciliated cells and other areas where the metaplasia in the form of squamous cells has persisted. I have never seen the return of goblet cells after ionization. The basement membrane is thickened and more dense. The tunica propria becomes thin due to an incomplete but definite paralysis of the parasympathetic system together with fibrosis. The glandular cells are in some areas destroyed with complete atrophy. Around the basement membrane of the glands is evidence of inflammation. The walls of the capillaries are thickened; sometimes the larger vessels are affected in the same way. In animals involvement of the periosteum and the perichondrium has been reported.

Ionization does have deleterious effects upon the mucous membrane of the nose. It should certainly not be used except after every effort has been made to secure a good result by simpler procedures. Our experience has been that if a proper study is made of the case of allergic rhinitis and if treatment based on this study is given, there are few cases in which ionization is indicated. Certainly it should be used only when the beneficial effects outweigh its deleterious action.

Sinusitis in Children

Edward C. Mitchell, M.D.

There are a few particular reasons why I became interested, almost twenty years ago, in paranasal sinus infection in children. Two of those reasons are present today: the first, Dr. Dean. He gave us the first clear concept that the paranasal sinuses acted as a focus of infection for many other conditions in children. The second reason I will best demonstrate by an x-ray of myself. For many years it has been necessary during the fall, winter, and spring for me to have my right antrum washed weekly in order to prevent headache, and particularly cough at night. I believe had I had attention in childhood this condition would not have occurred. The third group of reasons relate to the second. Childhood is the period of development. Although there is a strong hereditary influence in the growth, shape, and form of the paranasal sinuses, I still believe proper treatment early might modify some of the deformities. The shape of the face is determined to an extent by the development of the paranasal sinuses. Dental health and dentition are intimately connected with paranasal sinus development. The factors which influence growth and development must also play a part here: as the proper foods, in the broadest sense, include proper intake and absorption of the various mineral salts; required amount of sunshine; accessory foods, as the vitamins; adequate internal secretions from ductless glands (much has been said about this of late); and last but not least the early recognition and proper care of the allergic child.

Although speaking from a pediatric standpoint, I might be allowed to discuss the anatomy and to review the physiology or function of the sinuses.

Anatomy.—The paranasal sinuses are air cavities directly connected with the nares. They are lined with mucous membrane. The antrum and frontal sinuses contain columnar ciliated epithelium whose waves are directed toward the natural ostium of the sinuses. The mucous membrane of the maxillary sinuses particularly contain histocytes.

Physiology and Function.—It seems fairly well agreed that the sinuses are chambers for the interchange of air, that they warm the inspired air. They are especially designated to lighten the skull and give resonance to the voice. Shea and Mitchell have stated that the sinuses are an additional barrier together with the tonsils and other members of Waldeyer's ring against invading infection. In addition, the lymphatic drainage of the sinuses is into the cervical glands and thence into the chest glands.

Development of the Sinuses.—Present at birth are the maxillary and anterior and posterior ethmoids and, in addition, an infantile sphenoid which is present in the prebone tissue. It is claimed by many that the infantile sinuses are not aerated in many instances for several weeks. It is the general impression that the sinuses grow and develop by a process of pneumatization similar to the soap bubble, as described by Shea in one of his articles. Under normal conditions the frontal sinuses begin between the second and fourth year from a migration of ethmoid cells into the frontal bone. All sinuses, we believe, should develop in both size and shape if there is entire freedom from abnormalities which prevent their pneumatization. The sphenoids are usually developed by the tenth year. The antrums increase until at puberty they are usually below the floor of the nose. They broaden and take on a different shape as they develop. It is now generally believed that the antrums continue developing throughout life. The frontal sinuses likewise develop if pneumatization is not affected.

We believe that poorly developed sinuses can be attributed to one of the following causes:

1. Heredity (the shape of the face is in part determined by sinus development, and the sinuses most resemble those of the parent or antecedent of similar facial appearance)
2. Familial tendency, including environment
3. Infection
4. Allergy
5. Improper secretion of ductless glands.

These statements relative to the growth and development, we believe, are of importance to the pediatrist because it is our opinion that improper growth indicates interference with pneumatization and that an individual possessing this type of sinus rarely shows a normal sinus history.

Method of Diagnosing Sinus Infection, also of Differentiating Acute, Subacute, and Chronic Sinusitis.—History and general physical examination, including a rhinologic study, are necessary. Most of these patients come to the pediatrist with a condition foreign to the nose. In the acute stage it is fever, sometimes associated with coryza, sometimes not, usually a postnasal discharge, a red nasopharynx; except in the very young, there is often an associated redness and hypertrophy of the tonsils. In the older children this is seldom seen because the tonsils have usually been removed.

Transillumination usually shows dark sinuses. The x-ray film in the acute type without any history of former sinus infection shows the sinuses, as a rule, to be pneumatized normally. The treatment in this condition is to allay the inflammatory condition of the mucous membrane and reestablish proper drainage and ventilation. This is done by shrinking the mucous membrane of the nose, nasal packs, heat, rest in bed, and symptomatic and general care. In our experience fever from this type of infection may last several days. The subacute and chronic types of sinus infection may have acute exacerbation characterized by symptoms very much like the above—the differences, in our opinion, being that there is a history of former sinus disease and that in addition the roentgenogram shows improper development.

Before we leave the subject of acute sinusitis, we should note that hay fever and coryza incident to allergy should be included in this group, and that it should fall to the lot of the practitioner to manage properly the allergic disturbance, in addition to the local treatment by the rhinologist.

Chronic Sinusitis.—Rarely in my experience is the history such that it is at all suggestive of a focus in the upper respiratory tract. The child is admitted for many causes. In our list we have fever of undetermined origin, tuberculosis, return

of adenoid symptoms, nephritis, pyelitis, nervous manifestations sometimes as severe as chorea, rheumatic fever, various types of arthritis (I am showing a picture of a patient with arthritis deformans which lasted for a long period before sinus treatment was instituted and disappeared promptly after drainage), and sometimes loss in weight because of anorexia. Sometimes sinus infection produces trouble by extension to other parts of the respiratory tract—the ear particularly, with an associated otitis media and in some instances mastoiditis.

We have followed carefully many of these conditions due to sinus infection over a period of years, and we are still enthusiastic over eradication of sinus disease by the proper method which consists in the drainage of pus and the reestablishment of pneumatization by whatever means necessary. We have followed many children who did not improve before the sinuses were properly managed. The same children have shown not only improvement but in many instances complete cure after the sinuses were properly treated.

Tuberculosis, I believe, deserves particular mention. In the University of Tennessee Clinic for Tuberculosis in Children, we have more difficulty in differentiating tuberculosis from chronic sinus infection than any other condition. In order to determine whether tuberculosis even in the last stages was necessarily associated with sinus disease, we ran a series of roentgenograms of the chest and the sinuses of tuberculous children, many of them showing cavities; we found in most instances they had perfectly developed, well-pneumatized sinuses for the age, though they were in the last stage of tuberculosis.

Most all of the chronic sinus sufferers show some involvement of the chest glands because of the lymphatic drainage into this region. They often show a night cough, sneezing in the morning, sometimes night sweats, loss in weight, lack of appetite. The diagnosis is especially difficult when there is a mild tubercular reaction in old healed tuberculosis.

The child who is really a sinus sufferer and whose illness is confounded with tuberculosis is the type of child who, when he has proper local treatment of the sinuses and then general care on one of the tuberculosis farms, or open air schools, responds so rapidly.

Diagnosis.—Many of these cases are missed unless the pediatrist is "sinus conscious," and I do not mean in vulgar parlance a "sinus hound." There are still many practitioners who say that sinus infection plays little or no part as a focus in many of the diseases mentioned above. The physical examination should include a careful allergic history, a preliminary rhinologic inspection and x-ray films; if there is sufficient evidence, the case should be referred for rhinologic confirmation.

Treatment.—The treatment in our opinion should consist in reestablishment of pneumatization and evacuation of pus if the latter is present; this is accomplished by some means of opening the closed ostia. In chronic cases in which this ostium has been closed a long time, we believe that it is usually necessary to wash the sinuses. In older children this can be done under local anesthesia through the natural opening; in the young child our experience has not been so happy. We find that it requires a general anesthetic. First, we make an opening through the natural ostium; then, because of the fact that early in our series many of the ostia closed, it is advisable to make a counteropening under the inferior turbinate and to leave a tube in place. In several instances in which this was not done, the infection persisted because the ostium had closed.

When will paranasal sinus treatment improve the focal infection?

If treatment is given early before damage of organs occurs as a result of continued infection. For instance, a chronic tubular nephritis, or nephrosis, will not be benefited, but an acute glomerular nephritis will be cured.

When is the paranasal sinus condition considered cured?

1. When the original condition caused by the focus shows no symptoms.

2. When there has been no relapse.

3. When there are no evidences of sinus infection particularly in the winter following the sinus treatment.

4. When the sinus shows a return of growth and development as a result of reestablishing pneumatization (on this point we differ from some others).

I next show a series of cases in which there was poor sinus development at the age of nine years with some type of focal infection; there was perfect sinus development at sixteen or seventeen years of age with no sinus symptoms and no evidence of former focal infection. We also have the type of case in which sinus treatment was refused and in which there was in some instances evidence of persistent sinus involvement and no growth. That is the type of case which I believe in after years will follow a course similar to my own.

Roentgenograms should include the anterior and posterior view, the lateral and the chin-vertex positions, the idea being to obviate the petrous shadow. We use a modified Law position in children. The penetration should not be too great. We believe that by keeping a series of x-ray films of our sinus cases over a period of years for comparison, the same technic being used, we have accumulated some valuable information particularly concerning sinus development and time when the patient is entirely cured. We think transillumination is not of as much value in the child as in the adult because of lack of contrast.

I believe that many children suffer from both acute and chronic sinus infection and that the chronic type acts as a focus of infection and many times is overlooked. When the sinus is a focus of infection and the natural ostia are closed, the pus should be drained and pneumatization reestablished by surgical methods or by any other advisable method. I believe that sinus infection properly treated in childhood offers much more promise of complete cure than that neglected until adult life; that a properly pneumatized sinus is less likely to show symptoms of sinus involvement; that the expression, "Once a sinus, always a sinus," is not true; that proper treatment certainly benefits the condition and, if the infection is diagnosed early in childhood, offers to the individual freedom from lifelong sinus disease. As the upper respiratory tract is the most common entrance in all contagious and infectious conditions, close cooperation and study between the otolaryngologist and pediatrist are essential.

Suppurative Type of Sinus Disease

John J. Shea, M.D.

It is a pleasure to present the suppurative type of sinus infection in children, while Dr. L. W. Dean presents the allergic phase of this disease.

Nature has so organized the laboratories of our body that we first fight our infection in infancy with the adenoid and as we grow older, with the tonsil, which becomes the most active lymphoid tissue of the nose and throat. In the aged this selective localization is the cause of the activity of the lingual tonsil. Somewhere during the transition the sinuses develop sufficiently to aid in the battle of auto-immunization. If the tonsils and the adenoid are removed, this burden of auto-immunization is assumed by the sinuses. As long as the natural forces are able to maintain the proper immunity, the child remains well, but, when there occurs a bankruptcy of the immunization and a depression of the child's resistance, purulent discharge will be profuse with a blocking and retention of some of the discharge within the sinuses. Chronic sinus disease in children results from the failure to improve after a severe acute attack or the accumulation of many mild attacks.

The treatment of the suppurative type may be climatic, dietary or surgical.

Climatic Treatment.—A change of climate is useful for its beneficial effects upon sinus disease. Those in the mountains find improvement in seeking the level of the sea, while undoubtedly the children of the great Mississippi Valley are improved by a stay in the higher altitudes, unless the cold evenings predispose them to acute infections.

Dietary Treatment.—The diet low in sugar eliminates a product harmful to children with infections. It is necessary that their diets be well balanced, and that such foods as the mother and child have learned to avoid be omitted.

Surgical Treatment.—When to drain a child's antrum surgically is difficult to say. The attack upon empyema of the antrum in a child should be thorough, but radical surgery is seldom demanded. The local conditions and general manifestations must be carefully considered before advising drainage. The most vital consideration is the removal of a focus of infection. The roentgenologic study includes consideration of the present pathology and the morphology of the sinuses, for an arrested developed sinus lacks the resistance to combat infection. The procedure is not intended for treatment of an acute sinusitis except when the general condition of the child demands immediate relief from the infection. Local treatment with rest in bed and, when possible, hospitalization are first tried. My routine is to give the child three or four times a day a mixture of elixir of pyraminal and ephedrine, to pack the nose with a hypotonic salt solution, to exposure for twenty minutes to infra-red heliotherapy, and follow the heliotherapy by the instillation of phenolated nasal oil. The immunity is stimulated daily by omnadin, streptococcus antigen, or occasionally a blood transfusion. The use of suction with or without displacement is tried. Direct suction with a rubber catheter, after the method recommended by William H. Haskin many years ago, is of value in selected acute cases.

Anesthesia

If the child's condition warrants operation, ether is the best anesthetic because the operative procedure can be deliberate and thorough. In the cases with kidney disease either nitrous oxide or an ethylene mixture is safer than ether, though the operation is rushed.

Operation

The nares are cleansed by suction, and the site of operation is painted with a 30 per cent alcohol solution. The ostium of the antrum is sought and dilated. If it is not found, the membranous tissue of the middle meatus is perforated. The success of the operation depends on maintaining the patency of the ostium. Some of our earlier failures were the result of not appreciating the necessity of this second opening. A culture is made of the antrum. This is done through a straight trocar, with a syringe and a needle. If the patient is suspected of being allergic, sterile normal saline is used, otherwise brain broth medium is instilled and withdrawn. During the height of the phage craze, it was thought that leaving some of this medium within the antrum was of value, utilizing the sinus as an incubator for the growth of the phage, thus helping autoimmunization.

The nasoantral window is made with an antral trocar in the younger children and with a curved gouge in the older children. The aperture is then shaped to fit the rubber tube by a series of dilatations with Ritter sounds. The catheter is then inserted, with one of the smaller Ritter sounds used as an obturator. There is a characteristic feel when the catheter slips through the window. Suction is then applied to the drain. The appliance used consists of a medicine dropper, which visualizes the contents of the antrum. It is of value to note that air bubbles are freely mixed with the antral contents, for these bubbles denote the patency of the secondary opening. If no bubbles are visible, saline is forced through the tube until it appears in the back of the nose or nasopharynx, thus blowing out any plug

that might be blocking the ostium. Suction is again tried, and, if no bubbles are visible through the glass, the tube is removed and the steps of the operation are repeated—with special attention to the ostium.

Previous Tonsil and Adenoid Operation

It is rare that these children have not previously been subject to the removal of their tonsils and adenoid. The postnasal discharge coming from the sinuses promotes the regrowth of the adenoid. Whenever parents present their child to me with the statement that the child's adenoid has returned, I immediately search for sinusitis. The children with sinusitis, who have tonsils and adenoid, demand additional study, for the tonsils and adenoid precede the sinuses as immunizers, and the presence of sinusitis practically presupposes that the tonsils and adenoid are diseased. Seldom do I leave the tonsils and adenoid in situ, if I have to drain an antrum.

Postoperative Treatment

This has been simplified to keeping the tubes open and the instillation of a phenolated nasal oil about the tubes. Empirin compound is given at regular intervals according to the age of the patient, for it requires less to prevent a headache than to stop one. Many of the popular chemical antiseptics were tried by us as antral irrigations, but were discarded as of no particular value.

On the fourth morning the tubes are removed by instilling saline through them to aid in their expulsion. So far the treatment has been painless, and the child should not be afraid of the surgeon. The irrigations are continued until the discharge has ceased, and they are begun again any time drainage is impeded or if the opening has closed. The children are watched for a long time, and upon the return of the symptoms of sinusitis are treated by irrigations. In fact, it is advisable to irrigate these antra at the end of any acute infection of the sinuses and to remember that it is not the amount of sinus discharge that does the damage but that it is the lack of drainage with absorption of the discharge that harms the child. Since the ostium of a child's antrum is relatively larger than that of an adult, a small cannula can be used and the antrum can be readily irrigated.

The preparation of the autogenous vaccine requires a week, and during this time some form of antigen or protein therapy is administered to increase the immunity, thus assisting the sinuses in their fight against the infection. The autogenous vaccine is given consistently: one series during the fall, another during the winter, and

CHIEF COMPLAINTS FOR WHICH OPERATIONS WERE PERFORMED

	YEARS	
	1923-1925	1931-1935
Recurrent laryngitis and bronchitis (cough)	7	18
Nephritis (acute glomerular)	9	4
Pyelitis	7	3
Fever (acute pansinusitis)	3	11
Headache	1	7
Myocarditis (acute)	2	1
Dermatitis	1	1
Hypertrophy of pharyngeal and lingual lymphoid tissue	1	4
Neurotic children	4	2
Otitis media (chronic purulent)	1	4
Mastoiditis (acute purulent)	5	3
Arthritis (acute)	1	1
Cyclic vomiting	2	1
Asthma	7	7
Orbital abscess (acute)	1	1
Chorea	0	4
Bronchial lymphatic	0	3

a third series during the early spring, with sustaining doses whenever acute sinusitis threatens. When the pathologic condition has been thoroughly established in a child's sinuses, it requires one or two years of constant attention to reestablish the normal functions.

DISCUSSION

CHAIRMAN DEAN.—With extensive operation do the ethmoid cells ever re-form?

DR. SHEA.—I have no pictures of any that have done so.

CHAIRMAN DEAN.—New mastoid cells regenerate in the mastoid. The question is, do they in the ethmoid region?

DR. SHEA.—Any radical operation on the major sinuses arrests the development of that sinus.

CHAIRMAN DEAN.—Chronic purulent sinusitis in adults responds in an unsatisfactory manner to treatment. In childhood better results can be obtained.

DR. J. C. OVERALL (NASHVILLE, TENN.).—What would you think of the conjunctival test for sensitivity to protein, in place of the intramucosal test? I cannot say as to a comparison, but anyone can do the eye test.

CHAIRMAN DEAN.—There is such a thing as a local sensitization of the nasal mucosa. We shall try to see if the conjunctival test and the intramucosal test harmonize.

DR. H. H. PERLMAN (PHILADELPHIA).—I would like to ask about the high vitamin diet in the prophylaxis and treatment of sinus disease.

DR. MITCHELL.—Perhaps vitamin C in large amounts becomes a barrier against infection.

DR. OVERALL.—With a mixed infection in the sinus, do you separate the various organisms and test for individual sensitivity, or use all?

CHAIRMAN DEAN.—Repeated cultures are always made until uniform results are obtained. One or, at most, two organisms in repeated cultures will predominate, and we feel we can judge whether or not we are getting the correct organism. We prefer to use autogenous vaccine unmixed with stock vaccine.

DR. SHEA.—We use "seasonal cultures," making periodic collections from the prevalent upper respiratory tract infections, with autogenous vaccine.

CHAIRMAN DEAN.—We use pure autogenous vaccine. Of course, in four months or so, in chronic sinusitis the organism may change.

DR. T. J. McELHENNEY (AUSTIN, TEXAS).—What is the treatment of postnasal drip in sinusitis?

DR. SHEA.—Removal of tonsils and adenoids pushes the line of immunizer to the lingual tonsils or encourages the sinus to function as a protector in an immature state. Our procedure is to treat the nose locally, usually with antrum or ethmoid cell drainage. We shrink the membranes, pack the nose, and use infra-red treatments with packs in the nose. With much purulent discharge we use one of the solvents, as argyrol in glycerin, and displacement treatment, instilling salt solution into one side of the nose and using suction on the other. Finally we resort to the "glorified" treatment, surgical drainage with tubes in for three or four days.

DR. PERLMAN.—Do we not often overtreat the nose and produce a predisposition to sinus disease?

CHAIRMAN DEAN.—I do not, because I do not give many nasal treatments. Suction rather than douching is more popular with us. We do use in the active

acute stage a weak ephedrine solution in saline, perhaps followed by argyrol twice a day for a few days. Occasionally we will douche after several febrile days on the insistence of the pediatrician, but not for over two or three days.

DR. MITCHELL.—With regard to nose drops, we should remember the possibility of poisoning in using neosilvol over long periods.

CHAIRMAN DEAN.—In postnasal drip, we use ventilation for drainage and treatment for the general improvement of the child. Displacement therapy is used once a week if necessary.

DR. OVERALL.—I would like to ask about the use of iodized oil, as lipiodol, as a diagnostic measure.

CHAIRMAN DEAN.—I do not use it.

DR. SHEA.—I have used it very seldom. A good series of plates is just as useful. We use very few nose drops, and prefer normal saline. We do not use ephedrine, regarding it as a habit-forming drug—the membranes come to *demand* it. The benzedrine inhaler is useful for swelling of the upper air passages. We use estivin instilled into the eye and passing through the tear duct, in conjunction with the inhaler, to open the lower passages. With a pale boggy membrane, we use thyrocalx No. 1 (Mulford), a tablet three times daily for a child of eight or nine years, until 15 tablets are taken. This treatment helps to diminish lymphoid hyperplasia. We have the children take it twice monthly during the winter. We use cod liver oil in preference to any substitute.

DR. ROBERT BLESSING (EVANSTON, ILL.).—I would like to ask your opinion as to change of climate in sinus disease.

DR. MITCHELL.—I have seen children improve in Miami and the next winter have just as hard a time in Memphis. With treatment they get along all right in Memphis.

DR. SHEA.—In acute sinusitis a change to a warm climate is of benefit. In chronic sinusitis, it is not beneficial unless the whole winter is spent far south. I advise waiting until after Easter before returning to Memphis, to wait for warm sunshine.

CHAIRMAN DEAN.—Treatment by a warm climate is all right, if one rule is followed: the child cannot go away until good ventilation and drainage is established.

DR. McELHENNEY.—What do you say about swimming?

DR. SHEA.—I say "no." Cooling of the body surface is harmful. If the swimming is done in the warm ocean, I do not object.

DR. BLESSING.—Is the human upper respiratory tract constructed to tolerate water?

DR. SHEA.—No!

CHAIRMAN DEAN.—Children with sinusitis need exercise, hard play, and sunshine. I put cotton with lanolin in the children's ears to keep the water out and allow swimming. The child must be in a wet bathing suit not over twenty minutes and must not come out and go in again repeatedly. I encourage all exercise and outdoor play. Children can be taught to keep the nose out of the water.

DR. MITCHELL.—I put them in a sun suit and let them have it!

DR. J. R. LEMMON (AMARILLO, TEXAS).—What is your attitude toward the silver preparation and neosynepherin?

DR. SHEA.—They are used only as solvents and not as antiseptics.

DR. LEMMON.—We have no trouble with ephedrine. We are much bothered by dust storms. Our country is a paradise for the nose and throat man. We see the irritated and swollen nasal mucosa respond rapidly to a pack of 1 per cent solution of ephedrine. An acute upper respiratory tract infection and acute rhinitis that will show a duration of two weeks will show a shorter course if ephedrine is used. How does it cause any trouble?

CHAIRMAN DEAN.—Long-continued use of ephedrine makes ephedrine users. I am afraid of the habit. I have not seen an infant or child with the ephedrine habit, or the "hangover" that habitual users of the drug exhibit. I think we should warn adult patients against the formation of a habit. In children it is certainly useful in 0.5 per cent solution in acute cases, always used with the child on his back with the head tilted back. It should be used only for a short time. In the pediatric wards we use ephedrine solution, in twenty minutes apply suction, and then use argyrol.

DR. McELHENNEY.—What about the prophylaxis of sinus disease in the acute cold?

CHAIRMAN DEAN.—Keep the ostium of the sinus open. Some vasoconstriction may be used routinely as a prophylactic.

DR. J. B. SNOW (OKLAHOMA CITY, OKLA.).—Does a purulent nasal discharge mean sinus disease?

CHAIRMAN DEAN.—Not necessarily. The nasal mucous membrane can produce a purulent discharge. After five or six days of such a discharge, I would say that sinusitis is present unless there is a foreign body in the nose.

DR. ROLAND STAHR (FORT DODGE, IOWA).—What about the question of humidity?

CHAIRMAN DEAN.—I am a crank on humidity. The cilia mechanism must keep mucus moving, and with thick dry mucus present this cannot be done.

DR. LEMMON.—What about the effect of "air-conditioning" on the nose?

CHAIRMAN DEAN.—It is *too cold*, as I usually find it. There should be only a *slight* difference between the inside and the outside temperatures.

MEETING OF REGION III OF THE AMERICAN ACADEMY OF PEDIATRICS

On November 20 the state chairmen of Region III met at a luncheon at the Netherland Plaza Hotel, Cincinnati.

The next morning, following the scientific section of the program, the business meeting took place. The following order of business was adopted for the regional business meeting:

1. The meeting called to order by the regional chairman
2. Appointment of a secretary
3. Reports of the state chairmen
4. Committee reports
5. New business
6. Discussion of place of next clinical meeting
7. Election of officers of the Clinics for the ensuing years:
   (a) Chairman
   (b) Vice chairman
   (c) Secretary and editor.
8. Adjournment.

It was recommended that in the future, state chairmen be nominated by the individual state groups, then approved by the regional committee, and appointed by the president. This matter is to be brought before the executive board.

The possibility of having one panel discussion at the regional meetings was brought up.

Chicago was decided upon for the next annual meeting which will be held early in October, 1937.

On recommendation of the regional committee of Region III, Dr. Maurice Blatt was elected chairman, Dr. Stanley Gibson, vice chairman, and Dr. Heyworth Sanford, as secretary and editor.

A motion was made by Dr. Miner and seconded by Dr. Gengenbach that a vote of thanks be extended to Dr. A. Graeme Mitchell and his Cincinnati confrères for the splendid program which they presented and for their warm hospitality.

REPORTS OF STATE CHAIRMEN

Colorado is in the process of organizing its setup for the work to be carried on under the Social Security Act. A member of the Academy is chairman of the advisory committee appointed by the Colorado State Medical Society, to the State Department of Health, and five members of the Academy are on the advisory committee to the Maternal and Child Health Division of the work.

Colorado's share of the appropriation from the United States government which is matched by the state is of course based upon a comparatively small population widely scattered outside of Denver; the disbursing of these funds is in the hands of the state board of health.

A young pediatrician who has just completed two years of residentship in the Children's Hospital of Denver has been appointed by the state board of health as the assistant director of the Maternal and Child Health Division, to supervise the pediatric part of the program. Except for salaries, all the money will be spent in the rural and needy districts outside of Denver. It is planned to hold clinics and refresher courses in obstetrics and pediatrics for the local physicians. There is some division of opinion as to whether Colorado or out-of-state physicians should be appointed to do this work, and at the present writing no definite decision has been reached.

Franklin P. Gengenbach, M.D.
State Chairman.

Illinois

An executive committee has been appointed by the chairman. It is composed of representatives from each of the three medical colleges in Chicago, representatives from each community outside Chicago in which members are located, and members associated with the Chicago and state departments of health.

This committee meets twice yearly at the call of the chairman and its function is: (1) discussion of the policy of the Academy, and (2) formation of committees for the forwarding of this policy.

The first meeting was held Dec. 8, 1935. It was devoted to a discussion of Title 5 of the Social Security Act. Dr. Elizabeth Ball, of the Children's Bureau, Illinois State Department of Health, led the discussion. The following resolution was passed: The American Academy of Pediatrics, State of Illinois, offers the State Department of Health an advisory committee of five members with the chairman for the state as chairman of the committee. Dr. J. C. Kraft, Dr. Robert Black, Dr. Charles Schott, and Dr. Julius Hess were appointed. Dr. Clifford Grulee was appointed in 1936, following Dr. Schott's death.

Under the direction of the Academy, a pediatrics program was presented at the state medical meeting, in Springfield, May 19, 20, 1936. The scientific meeting was led by Dr. John Vonachen, chairman. In addition to the papers in its own section, one or more were presented by the members before each of the following sections: public health and hygiene; medicine; radiology; surgery; and eye, ear, nose and throat.

A meeting of the Academy members was held following the scientific section, when the request for a child welfare (older children) book by the director of the Department of Public Welfare was presented. The Academy agreed to produce such a pamphlet. It was thought that funds might be made available from money set aside for the health of the children of the state. The director of the Department of Public Health had at that time a tentative agreement with the Children's Bureau for funds for a refresher course.

Two systems of presentation of these courses were recommended by the Academy:

A. To groups of physicians as an organized postgraduate course, given in Chicago, with the following committee in charge: Drs. Irish, Hess, Brennemann, Arthur Abt, Grulee, and Black.

B. By group lectures before county medical societies, with the following committee in charge: Drs. Crawford, Calvin Spivak, Vonachen, Elkhammer, Stulik.

(The work of both committees is to be coordinated by the advisory committee of the Director of Public Health. Programs for this work are in process of preparation.)

On Nov. 15, 1936, a conference was held with the Director of Public Health, Dr. Frank Jirka. The following is an analysis of the state organization, which is cooperating 100 per cent with our organization and with the Illinois State Medical Society.

I. Maternal and Child Welfare (Social Security Bureau) $80,000 matched funds from the Children's Bureau.

A. Administration

Full-time director, selected by the Chicago Gynecological Society, salary $4,500; with one assistant, two dentists, four field physicians, 15 nurses. Salary of physicians $3,600, plus traveling expenses.

B. Function

1. Postgraduate course to county societies
2. Education of lay public
3. Prenatal care.

(In cooperation with County Medical Societies.)

II. United States Public Health (Social Security) $250,000 matched funds.

A. Administration

23 districts outside Chicago.

B. Personnel

1 physician, 1 secretary, 1 nurse, 1 sanitary engineer, 1 dentist. Physician's salary $3,600 plus traveling expenses.

C. Function

Prevention and control of infectious disease (I believe this is the organization which will carry on the antisyphilis program).

III. Commission for handicapped children.

A. Origin

Created in 1929 by Illinois statute and under the department of Public Welfare. Funds $111,000 matched.

B. Personnel

Director of Public Health, Superintendent of Public Education, Director of State Welfare, 3 orthopedic surgeons and several civic-minded business and social workers. No pediatrician and 3 orthopedic surgeons. I have requested that a pediatrician be appointed and think that he will be.

This is the administrative unit for line bureaus of which orthopedics is in immediate contemplation.

Subcommittee on orthopedics: Drs. Thomas, Campier, Foley, Warner, and Kepick.

To be formed—special committees on line bureaus including the following aspects: heart, neuropsychiatric, tuberculosis, blind, deaf, and diabetic.

C. Administration

Orthopedic surgeon and pediatrician to be appointed on orthopedic line at once.

D. Function

To carry out Part 3, Title 5 of the Social Security Act.

IV. Infantile Paralysis Commission.

A. Origin

Formed in 1934 at the request of Dr. Jirka.

B. Administration

State funds.

C. Personnel

Research workers, orthopedic surgeons, serologist, pediatrician to be added.

D. Function

1. Organization of serum centers
2. Collection and distribution of convalescent serum
3. Instruction to 15 local physicians in early diagnosis, preparalytic stage. Result excellent.

V. Activity of the Society has continued through lay education by the Educational Committee of the Illinois State Medical Society: broadcasting, newspaper items, programs for country societies, libraries, State Baby Book, and in cooperation with the Parent-Teacher's Association addresses and the yearly roundup.

At Dr. Jirka's request the executive committee advised on the public scarlet toxoid and pertussis vaccine as follows: Both should be considered as still in the research stage, not yet ready for public health recommendation.

The Committee decided to call Governor Horner's attention to the insufficient number of pediatricians on state committee. It also recommended that in lay talks the groups be asked to pass resolutions on the care of handicapped children. Such resolutions to be forwarded to the governor, stating the number of individuals who so recommended.

Recommendations: That the director of Region III thank and compliment Dr. Frank Jirka on the work he is doing for the children of the state and the cooperative spirit in which it is done.

That also a similar letter of appreciation be sent to the educational committee of the state medical society for their planning of popular and professional programs advancing pediatric knowledge.

Maurice Blatt, M.D.
State Chairman.

Indiana

The Academy has made an effort in Indiana to enlist all those who are eligible in the Academy and urge that they qualify for the Board of Pediatrics.

We have organized in the state a state pediatric society and through this we are trying to help educate the pediatricians of the state. We have worked through the state and we have this at a stage where it conforms to the American Academy requirements. One of our number has charge of the state Health Department, and the Academy has excellent liaison with this department.

Postgraduate teaching throughout the state is being done through hospital staff meetings, county medical societies, and district medical society meetings. We are doing this by groups upon request.

We have maintained in our state an active speaking bureau which can furnish speakers to lay organizations, such as the P. T. A.

Much of the educational work in the future may be taken over by the Social Security setup through our health department but as I have said before, Dr. Mettel, one of our members, is chief of this department.

Matthews Winters, M.D.
State Chairman.

Iowa

The activities of Academy members in Iowa have largely been associated with Part I of Title 5 of the Social Security Act. This division is under the administration of the state department of health and in addition to the Director of the Bureau of Maternal and Child Health has employed a full-time pediatrician to assist in the work.

Immunization programs are being carried on in some twenty-two counties in which the need has been shown to be greatest. The cooperation of the medical societies in each of these counties is secured and the individual members administer the preventive agents.

In one county a demonstration of all phases of maternal care has been set up, and is in operation at the present time.

The Committee on Child Health and Protection of the Iowa State Medical Society, of which three members are also members of the Academy, has met on several occasions with health department officials and has assisted in organizing and carrying out the plans of this phase of the Social Security Act.

The Crippled Children's Division is under control of the Board of Education and is being administered by the medical department of the State University of Iowa. The orthopedic part is under the direction of Dr. Steindler, and Dr. Boyd of the pediatric department is directing the pediatric part. Up to the present Dr. Boyd has confined his activities to a follow-up of patients with syphilis, diabetes, and rheumatic heart disease who have been at one time or another patients in the Children's Hospital. Later on it is probable that diagnostic centers will be set up in various rural areas in the state for the detection of crippling defects of both orthopedic and the types mentioned above. In this work the pediatricians will be called upon to conduct many of the clinics.

The division relating to child services is not in active operation in Iowa at present.

Following the request of Dr. Roberts, chairman of the Committee on Child Relations of the Academy of Pediatrics, the state chairman of Iowa has appointed four Academy members to serve as advisory committee to the administration officials of the three services under Title 5. The members appointed are Dr. Robert McBride, Sioux City, Dr. Roland Stahr, Fort Dodge, Dr. Fred Moore, Des Moines, and Dr. Hill, Des Moines.

We are also organizing refresher courses in pediatrics for the general practitioners of the state. These courses will be given by members of the state pediatric society, and should get under way sometime after the first of the year.

Lee Forrest Hill, M.D.
State Chairman.

Kansas

There is really nothing very definite to report as to the activities of the Academy in Kansas. We have incorporated, and I have attended two meetings at Topeka with the Maternal and Child Welfare Organization of the federal government.

Paul C. Carson, M.D.
State Chairman.

Michigan

Starting the year of 1936 with a strong and willing organization, the Michigan members of the Academy of Pediatrics have been able to accomplish much more than had been possible in previous years.

The maternal and child health program under the Social Security Act in Michigan is under the direct charge of one of our members, Dr. Lillian Smith. Our first meeting with Dr. Smith was held March 17, 1936, in Detroit. At this time the tentative program was discussed and certain unsatisfactory features were eliminated from the program as a result. Dr. Smith has been very cooperative, and matters pertaining to pediatric problems are submitted to the Academy members for their recommendation. Dr. L. F. Foster, Dr. F. Miner, and Dr. R. Kempton have been appointed a committee for the Academy members to aid Dr. Smith.

April 20-21-22, 1936, the three-day postgraduate conference on pediatrics was held at the Children's Hospital of Michigan in Detroit. This has become a yearly feature of the Academy program in Michigan and has proved extremely successful. Sixty-six physicians, most of them in general practice, attended and were enthusiastic about the program. The members of the Academy have been extremely cooperative in making this conference successful, especially Dr. J. A. Johnston, Dr. D. J. Levy, and Dr. T. B. Cooley, who have acted as a committee in arranging the program.

Three meetings of the members have been called during the year. The first was held Feb. 19, 1936. Twenty members were present. Among the subjects discussed were: the social security program in Michigan; the pediatric section of the Michigan State Medical Society; radio programs; postgraduate teaching; appointments to committees of the state and county medical societies, and appointments to the filter committees of the probate courts under the Afflicted Child Act.

The second meeting was held July 17, 1936, at the Detroit Boat Club. This meeting was devoted to a conference with Dr. Lillian Smith on the maternal and child health portion of the Social Security Act.

The third meeting was held Sept. 23, 1936, at the Hotel Statler in Detroit. At this meeting the postgraduate work of the state medical society was discussed. Reports of the committees cooperating with Dr. Smith and the state medical society and the committee for postgraduate instruction were read.

In the field of undergraduate medical education the Michigan members have brought about a complete reorganization of the pediatric department at the Medical College of Wayne University.

Dr. T. B. Cooley has accepted the chair as Professor, and under his influence the department of pediatrics is being developed so as to utilize the facilities of the Children's Hospital of Michigan and to bring the standards of the department to a point where the instruction will far surpass the minimum recommendations of the committee on undergraduate instruction of the White House Conference.

Plans are being discussed which we believe will result in the establishment of postgraduate teaching leading to the degree of Master of Science and will be acceptable to the Board of Pediatrics.

In the field of lay instruction the radio has been a very useful means of furnishing information on pediatric problems to parents.

In addition to a weekly program broadcast over the Michigan radio network, the influence of the Academy has resulted in the inclusion of pediatric subjects on the state medical society programs. We are preparing material which is sent to the county medical societies for broadcasting over local stations throughout the state.

The joint program of the Academy and the National Congress of Parents and Teachers known as the Radio Forum is carried by eight stations in Michigan but to date we have not been able to secure a Detroit outlet.

Meetings have been held with the Detroit Council of Parents and Teachers and the Trendle Broadcasting Company, and it is hoped that in the near future the forum will be available over a Detroit station.

We are fortunate in having as a member of the Academy, Dr. L. F. Foster, the secretary of the State Medical Society. The pediatric section of the state society is under the leadership of Academy members in the persons of Dr. Carl Dengler, chairman, and Dr. Ward Chadwick, secretary.

During the year a questionnaire sent to all members showed that our members hold forty-one appointments on committees of the state and local societies and hold seventeen offices in these societies.

All members of the Academy from Michigan in practice hold appointments at recognized hospitals.

During the year there were 225 pieces of mail passed through the chairman's office on matters pertaining to the Academy not including the local committee work.

Annual State Plan for Maternal and Child Health Services in Michigan

(12 months ending June 30, 1937)

A. How the seven requirements for state plans under the act are met.

1. Financial participation by the state.

This participation includes $34,460. State appropriation for the Bureau of Child Hygiene and Public Health Nursing for the year ending June 30, 1937; $3,000 for clerical work in the Bureau of Records and Statistics for recording births, infant and maternal deaths; $8,000 for preparation and distribution of toxoid and other biologics by the Bureau of Laboratories for the protection of children from certain communicable diseases; $3,250 for preparation, printing, and distribution of communicable disease literature and for special investigations of communicable diseases by the Bureau of Epidemiology; $56,250, or three-fourths of the total amount available for county and district health units from the state (this amount is thought to be a reasonable estimate of the amount spent in activities for mothers and children of the $75,000 total appropriation for county and district health units from the state). The budget submitted with these plans shows how state funds are to be used in carrying out the plan.

2. Administration and supervision of the plan.

Administration and supervision of the plan will be made through the Bureau of Child Hygiene and Public Health Nursing by the director of the bureau, chief of the Division of Public Health Nursing, consultant in Maternal and Child Health Nursing, two district nursing supervisors, and other members of the present staff.

Among activities already in operation are the following:

a. Women's classes in rural areas.

b. Child care classes in rural schools.

c. Prenatal nursing programs.

d. A special prenatal nursing program by two nurses in one county with relatively high maternal mortality and no other county nursing program.
e. Maternal and child health nursing programs in five counties which previously had no generalized public health nursing program.
f. Preparation of a film on prenatal care by the maternal health committee of the Michigan State Medical Society.
g. Training of six nurses in public health at the University of Michigan.
h. Supervision of public health nurses throughout the state.
i. Distribution of prenatal letters and other literature.
j. Distribution of certificates of registration of birth.

Among new activities for the year ending June 30, 1937, will be the following:

a. Expansion of all the above activities.
b. Financing the giving of lectures by local physicians on prenatal care accompanied by a film on prenatal care, the film and lectures to be prepared by the Maternal Health Committee of the state medical society.
c. Institutes by the University of Michigan in which obstetrics and pediatrics are featured.
d. Refresher courses in obstetrics and pediatrics in certain areas of Michigan.
e. Locating nurses in new areas to carry on other intensive prenatal programs or maternal and child health nursing as the need arises. This plan includes the placing of nurses now being trained in public health at the University of Michigan.

3. Methods of administration.

Administration of the entire program will be through the Bureau of Child Hygiene and Public Health Nursing. Supervision will be carried on directly by the personnel named in A-2, and in organized county or district health units where assistance is given in developing maternal and child health services, additional supervision will be given by the county or district health officers.

Activities already in progress are as follows:

a. Women's classes.

These classes are taught by two staff physicins, usually in rural areas. They consist of a series of eight talks and demonstrations on the care of mothers and children, and a copy of the outlines used and distributed to the women taking this course accompanies these plans.

b. Child care classes.

These classes, taught by staff nurses, consist of talks and demonstrations on infant and child care. They are organized in schools, mostly rural, and include approximately twenty classes once a week for twelve weeks.

c. Prenatal nursing programs.

These programs are conducted by staff nurses and include supervision of prospective mothers during pregnancy, cooperating with the attending physician. Advice is given to mothers on diet, exercise, and general hygiene of pregnancy, with instructions as to supplies and preparation for home delivery. Reports are sent to the attending physician, and every effort is made to keep the patient under the regular supervision of her physician. Following pregnancy, mother and child are kept under nursing supervision until at least the sixth or eighth week, and the mother is encouraged to go to her physician for a final check-up following delivery.

d. A special prenatal nursing program is being carried on in St. Clair County, which has a population of 72,076 and a maternal mortality rate of 7.25. Two nurses have been assigned to the county, and an advisory committee of five physicians has

been appointed by the county medical society. The only public health nursing service in the county consists of one city nurse in St. Clair and one school nurse in Port Huron.

e. Maternal and child health nursing services are being carried on by staff nurses in the following counties: Kalamazoo, Montcalm, Clinton, Gratiot, Muskegon, Lapeer, and Tuscola. These services include calls by the nurses on prospective mothers, mothers of infants and preschool children, together with special services in schools such as inspection of children referred by the teachers, with follow-up in the home to encourage examination and treatment, if necessary, by the family physician. Also in the schools, inspections will be made if any communicable disease develops, and child care classes will be taught occasionally. So far, only one nurse has been assigned to each county, but it is hoped to supplement this with additional nurses as the program develops and if funds are available.

f. A film is in the process of preparation at Harper Hospital, Detroit, under the direction of the Maternal Health Committee of the state medical society, to which the bureau is contributing $350 for the original film and $50 each for three extra films, a total of $500. Requests have already been filed for presentation of this film by local women's clubs, and it is at the request of the State Federation of Women's Clubs that this plan is being developed.

g. The bureau is financing the training of six nurses in public health at a special course being given by the University of Michigan. This course consists of three months' theoretical training and one month's field experience. At the close of the course, the nurses will be added to the staff of the bureau, some to develop maternal and child health programs in counties, and some to teach child care classes in schools. A tuition fee of $60 has been paid for each of these nurses, in addition to $100 a month living expenses.

h. Supervision of public health nurses is being given by the assistant director of the bureau, who will become chief of the Division of Public Health Nursing July 1.

i. Distribution of letters on prenatal care and other literature. The letters include nine letters to prospective mothers on prenatal care and one letter on postnatal care.

j. Distribution of certificates of registration of birth. These are distributed to parents of all legitimate babies born in Michigan each year and are accompanied by a small pamphlet, "Message to Parents." The certificates are distributed in the homes by nurses in organized counties and in some cities, by staff nurses as part of the maternal and child health service, or, when not delivered personally to the homes, by mail to the parents.

The plans include several changes for the coming year. A division of public health nursing will be organized in the Bureau of Child Hygiene and Public Health Nursing, with the present assistant director of the bureau as chief of the new division. She will supervise public health nurses in the state, with special attention to public health nurses maintained in part or entirely by the counties, and to those nurses in county or district health units to which the state contributes financially.

A consultant in maternal and child health nursing has been appointed who will be directly responsible to the director for program plans, will supervise the maternal and child health nurses on the bureau staff, and will work with field nurses in organized and unorganized counties in developing maternal and child health services.

An additional woman physician will be added to the staff to assist in administration and supervision of the program in office and field.

University of Michigan Institute.—Plans are under way for cooperation with the University of Michigan through special institutes to be held in certain districts in the state, in the course of which institutes lectures will be given on subjects related to maternal and child health. Details as to the location of said institutes, the number of lectures, and personnel, are not yet available but will be submitted within a

week or ten days. There will be a per diem allowance of $25, plus expenses, to the physicians who give the special lectures. The plan is being worked out with Dr. James D. Bruce, vice-president of the University of Michigan and dean of postgraduate medicine. The sum of $2,500 has been budgeted for this purpose.

Financial assistance will be given the state medical society maternal health committee in the preparation of a film on prenatal care and in the giving of lectures to accompany the film, the lectures to be given to lay groups by local physicians and by staff physicians. Physicians not on the staff will be paid living expenses not to exceed four dollars per diem, and five cents a mile for travel. A total of $2,288.66 has been set aside for this purpose. The film will be the property of the Michigan Department of Heath.

Plans are being considered for refresher courses in obstetrics and pediatrics, but they are still incomplete. The plan is to organize such courses in certain areas especially in need of such courses, to be given by a recognized authority on these subjects. The fee will be approximately $25 a day and expenses, and the sum of $3,900 has been budgeted for this purpose.

Plans are also being considered for a maternity nursing service in a county with a relatively high maternal mortality. The county in mind is Montcalm, which has a population of 27,471, a maternal mortality rate of 8.43, only one maternal and child health nurse in the entire county, and no other public health nursing service. Of the 517 deliveries in 1935, 64 were hospital deliveries and 453 home deliveries. It may be necessary to precede this service with a prenatal educational nursing service until plans may be completed for the more complete service.

Extension and Improvement of Local Child Health Services.—Continued cooperation with the State Congress of Parents and Teachers in the summer round-up of the children, assisting maternal health committees of county medical societies in studying conditions related to maternal and child health and in planning ways to improve such conditions, making studies of local conditions and stimulating local action to improve conditions, assisting already organized maternal and child health services: these and other similar activities are included in the above heading.

Under "Activities Already in Progress," the demonstration service in St. Clair County has been mentioned, in which two nurses have been located in the county to do intensive work among prospective mothers and to give demonstration postnatal care where necessary. The nurses secure standing orders from each physician as to instructions to be given routinely to each of his patients, send him a written report on each patient visited, and discuss with him any special instructions for individual cases.

Mention has also been made of a proposed maternity nursing service in Montcalm County, where it is planned to locate four nurses to give nursing care at time of delivery to those patients unable to provide such care, in addition to the routine prenatal and postnatal educational program. Supervision of both of these services will be through the state health agency and its nursing supervisors.

Minnesota

The chief new activity in Minnesota during the past year was the planning and administration of the policies of the federal Social Security Act, by the Maternal and Child Welfare Bureau of the state board of health.

The board of health appointed an advisory committee on which the official pediatric representatives are your regional chairman and your state chairman. After due consultation with this advisory committee, the state board of health laid down a broad policy for future action under the Social Security Act. Your chairman is in full accord with this policy and its actual administration by the Maternal and Child Welfare Bureau. The state board of health is in full accord with our ideals

and is carrying them out without being unduly hampered by political considerations. Your official representatives are and will continue to be in close touch with the situation, to see that the long range interests of the children of the state are conserved.

The activities of the Federal Crippled Children's Division in the state are being administered by a pediatrist who is working in close touch with the pediatric department of the Medical School of the University of Minnesota and with your state chairman.

Close cooperation with the extension division of the state university, the Minnesota State Medical Society, and the Minnesota Public Health Association is being maintained in providing lectures to the county medical societies and demonstration clinics to lay groups in the rural sections.

Minnesota has an unusually broad and forward-looking program for guarding the interests of its children, and I feel our function should be that of cooperation and consultation with the official state agencies in the field rather than the initiation of an independent program of our own.

E. J. Huenekens, M.D.
State Chairman.

Nebraska

We have been carrying on with the school health advisory work in Omaha as previously reported. In connection with this, examinations of all school children for deafness has been carried out, also demonstration work in the schools by a trained dietitian, in feeding of children. Children under the federal relief roll have been chosen for this work. At the present time we are undertaking a survey of the subnormal children in the schools.

Dr. Hancock was appointed as representative of the Academy to the maternal and child health setup of this state.

Dr. Hancock's Report.—The maternal and child health work has been very slow in getting started because of the difficulty in finding a director. That problem has been solved to the great satisfaction of all concerned by the appointment of Dr. Bell. The medical relations of this part of the program are being taken care of by the Maternal Health Committe of the state medical association. They have been consulted at every step, and I can assure you that nothing will be done without full medical approval. I have been present at all the meetings of this committee. No actual work has been done as yet, but the plans include subsidization of maternal and child health work in demonstration county health education, maternal and child health units, postgraduate work in obstetrics and pediatrics, health education, maternal and child health, nursing, and similar activities. No treatment or even clinic work is contemplated at present.

The crippled children's work is being carried out by the Department of Child Welfare. There has been little or no pediatric participation, for several reasons: the work is limited to orthopedic cases; the regulations require a diagnosis by an "orthopedic surgeon" before the case is taken over by the state; there is no medical advisory group, and no medical director at present. I would be very glad to obtain some information on the pediatric aspects of this program in other states.

The child welfare program is being carried on by the Department of Child Welfare as a strictly social activity. There has been no medical participation except in individual cases.

It would seem from the above that the Social Security Act is being pretty much ignored by the doctors in Nebraska. As a matter of fact, there has been a good deal of medical advice, mostly on a personal basis. I have myself spent many hours

with the workers in these activities, entirely unofficially, but with some good results, I hope. It seems to me that our first job is to convince the profession that they must take an interest in these social movements.

Clyde Moore, M.D.
State Chairman.

North Dakota

All details given are not in the true sense accurate information by true government statistics because at present these are not available.

So far as I was able to learn, it is believed that the population of the state will be 65 per cent on relief during the winter. This relief, of course, also includes A.A.A. check on farmers for not planting, rather than just considering the condition caused by the drought. This has made a situation very ripe for the beginning of the Social Security Program: in fact, the medical profession as a whole has felt that there must be a definite program, outside of the politics of the various counties, to handle the situation as it exists.

Several weeks ago the committee of economics for the state medical society was called in to Bismarck by the federal government manager of relief, E. A. Willson, and resettlement administrator, Howard Wood, to discuss ways and means of aiding the medical profession in the handling of relief. The proposition offered and accepted was that of the formation through the sponsorship of the federal government of a society to be known as the North Dakota Farmers' Mutual Aid Corporation. I will quote briefly from the letter sent out by the resettlement administration to each physician in the state.

"On October 8, 1936, the North Dakota Farmers' Mutual Aid Corporation was incorporated under the laws of North Dakota for the purpose of providing emergency medical and emergency dental care to standard and grant clients and emergency grant clients of the Resettlement Administration in North Dakota. Standard farm plan clients and emergency grant clients of the Resettlement Administration will be eligible for such emergency medical and dental care if they have made application for membership in the North Dakota Farmers' Mutual Aid corporation and not otherwise. Therefore, applications for membership in the North Dakota Farmers' Mutual Aid Corporation should be secured from all standard and emergency grant clients of the Resettlement Administration as soon as practicable. Only standard and emergency grant clients of the Resettlement Administration are eligible for membership. No membership fee is required. But no loan for emergency medical care or emergency dental aid will be extended by the North Dakota Farmers' Mutual Aid Corporation to any resettlement client who has not applied for membership."

This is a definite step in the direction of socialized medicine, but under prevailing conditions there is no alternative in North Dakota, and I might add that I believe the doctors as a whole are generally thankful that such a step is being taken. One or two years of good crops in the state would reverse the entire situation and mental attitude of the public at present; however, when you realize that for a number of years everything has been getting worse instead of better, it should be easy for you to understand just why the state society is taking that step. There is only one factor about it that is too bad and that is that the doctor who has most to do with the results of the program is not truly in charge. An attempt was made to represent the medical profession by naming a qualified physician, Dr. Bodenstab, of Bismarck, to act as referee, but this is more to assure those in charge of relief funds that neither the patient nor the doctor is abusing the privilege.

The group representing the doctors in the obstetric or maternal health group of the state society has been very active in attempting to carry on the program of instruction for the general practitioner as outlined by social security and I believe in

every way has attempted to cooperate with Dr. Maysil Williams, who is state health officer and, therefore, direct representative of the federal government in this health program in our state.

My personal feeling is that the doctors have failed to take advantage of this work and show a decided lack of interest by failing to attend the programs as they were arranged. There are two factors that may have influenced this: the first is the difficulty with which a practitioner finds time to leave his work to attend such meetings and the second is the feeling among physicians that there must be some ulterior motive in such a program. It is quite evident that the medical profession as a whole has either failed to grasp the definite trend of events or else is hoping by its lack of cooperation to stall its progress. My personal fear is that unless the doctors cooperate on this program, the condition will be forced upon them through the education of the public, and we will be in position of taking orders rather than assisting in giving them.

The pediatrics group of the state society in North Dakota is not very active as yet. The committee was appointed by the state medical president early last summer, and as yet we have not met. Dr. Conrad, of Jamestown, was appointed chairman. The preelection lull had much to do with lack of progress in this program from our point of view, and I feel sure that unless Dr. Conrad is more interested in obstetrics than pediatrics, we will have a very definite program with beginning progress to report to the next meeting of Region III of the American Academy of Pediatrics.

R. E. Pray, M.D.
State Chairman.

Ohio

The members have not been called to any special meeting because the 1936 district meeting was scheduled to meet in this state. The entire state membership was contacted by letter early in the year to elicit attitude of the membership toward the Social Security Program of child welfare and maternal hygiene.

The individual members very generally responded by declaring themselves willing to cooperate in this educational program. Four members of the Academy were present at the advisory council meeting at Columbus, called by Dr. Van Horn and Dr. Hartung to cooperate with the state obstetrical society. The skeleton program included a special effort to improve prenatal care in one of the five counties and a survey of schools to ascertain prevalence of mottled enamel.

The program concerns itself most with the preparation of nurses and physicians to conduct intensive studies and demonstrations in counties where the medical units are less organized. All of the effort is to be waged with the cooperation of the county societies; at least two full-time pediatricians will be employed for direction of this work. About $135,000 will be used in 1936-37 in the initial effort.

Dr. Van Horn has distinguished himself so much that Dr. Eliot has found need of using him in national capacity as state consultant. This is our temporary loss. He will no doubt be replaced by the time this report is read. The membership in this state is still incomplete since several eligible physicans have not applied for membership. Every effort is being made to assist them in this regard.

Suggestion: Many desire a return to case presentation type of program for regional meetings; at least half of the papers might be case reports. Others desire a part of the program to be in the nature of panel discussion. This would give many that miss the annual national meeting a bit of program embracing discussion and would allow for men from various cities to participate.

Sterling Ashmun, M.D.
State Chairman.

South Dakota

Since April 23, 1936, when social security funds were made available to the state welfare commission, about 160 crippled children in South Dakota have been hospitalized for corrective measures. These children would have otherwise been unable to secure aid in correcting their deformities. There are three nurses doing crippled children's work in the field.

Up to the present time, twenty-five counties will have generalized public health service. There are four public health units: one supported entirely from maternal and child health funds; two, each with its own unit, supported entirely from United States Public Health Service and local funds, and one financed jointly from Public Health Service, maternal and child health, and county funds.

In a cooperative project between United States Public Health Service and Maternal and Child Health Division, eleven counties have allocated county funds and are receiving matched federal money for a generalized public health nursing service.

Postgraduate courses in obstetrics and pediatrics were given in ten cities in the state during June and July.

Every county and district medical society as well as our hospital staff meetings are devoting more time to pediatrics.

Since there are only two Academy members in our state it is impossible to do more than just work with these other organizations. I wish there were more we could do, but I hope our efforts are not in vain.

Goldie E. Zimmerman, M.D.
State Chairman.

Wisconsin

The funds provided by the Social Security Act are administered by three different agencies in Wisconsin:

1. The Juvenile Department of the Child Welfare Division of the Board of Control.
2. Crippled Children's Division of the Bureau of Education.
3. Maternal and Child Health Work of the Children's Bureau, a division of the state board of health.

The phase of these activities in which medical men have participated most actively has been that concerning maternal and child health work under the direction of the Children's Bureau of the state board of health. A quotation from the letter of Dr. Janney, one of the participants in this course: "In the review courses given for Wisconsin physicians in obstetrics and pediatrics this summer under the National Security Act, 58 counties were covered.

"In pediatrics an attempt was made to show, by reviewing statistical studies, the need for and possibilities of lowering the infant morbidity and mortality rate. Prematurity, neonatal conditions, infant feeding, immunization and the care and management of older children were reviewed in as practical a manner as possible. Rheumatic disease and tuberculosis were covered in some detail. Mimeographed outlines of the reviews were given out. Slides and motion pictures were used extensively.

"The reviews were made as informal as possible and part of the time was given over to discussion and questions. Most of the 676 physicians who attended were from rather isolated rural areas and seemed generally interested. This number represents a little over 50 per cent of the men in the district."

The local members of the Academy have again given active support to several activities in the child welfare field conducted by the local county medical society.

The Child Welfare Committee of the Milwaukee County Medical Society organized a preschool roundup for the examination of all children on social agencies' or relief rolls. Almost one hundred physicians participated in this program. This preschool roundup took the place of the usual immunization drive sponsored by the county medical society.

A. B. Schwartz, M.D.
State Chairman.

ABSTRACTS OF PAPERS PRESENTED

Use of Supravital Technic in Studying Children's Diseases

Clare R. Rittershofer, M.D.

The supravital technic has been of value in a group of selected cases involving the identification of early forms of myelocytes, as in acute myeloblastic leucemia; in cases in which differentiation of mild conditions must be made from malignant diseases, as between pertussis on the one hand and the lymphocytoses from leucemia and lymphosarcoma on the other. In suspected tuberculosis a careful study of the monocytes may show the changes characteristic of that condition and thus lead to an earlier diagnosis. In other diseases in which the monocytes are abnormal, as monocytic leucemia, the method has been of great value in positively identifying these cells. In conditions in which moist preparations are essential in making the diagnosis, as in sickle-cell anemia or in ordinary sickling, the skill acquired in the use of the supravital technic aids in the better interpretations of those preparations. In malaria, moist films are preferred by many people as an added check against false interpretations of platelets and artefacts which may overlay the red cells. It is easy to detect faint traces of hemoglobin which occur in the young red cells and which are usually concealed on the fixed smear by the intense basophilic staining. With the supravital technic the recognition of the greenish yellow color of hemoglobin simplifies the differentiation of young red cells from young leucocytes with which they may occasionally be confused.

The method is not used for the routine study of blood but only for those cases where additional aid is needed.

Significance of the Albumin Globulin Ratio in Nephrosis

Howard W. Robinson, M.D.

The decrease in the blood serum albumin globulin ratio of nephrotic patients is well recognized and is used as confirmatory evidence in the diagnosis. In many cases, for long periods, the patient's serum shows a marked reduction in the total protein concentration and an albumin globulin ratio below 1. It is reasonable to assume that such a patient affords a nutritional problem, and attempts should be made to give a protein diet that would meet the body needs and to balance loss in the urine. Increase in the serum protein level should be an indicator of such progress. Generally, the elevation of serum protein takes place very slowly, and many determinations are made that show only small changes.

From determinations of serum protein and protein partition, by Howe's method using the 22 per cent sodium sulphate solution at 37° C., it has been observed that the patients appear much better after increases have been obtained in the albumin concentration. Often, after increases in total serum protein that were due entirely to an increase of the globulin fraction, the patient has shown no general improvement. At times we have obtained reductions in the globulin concentration that lowered the total protein, raised the A/G ratio and caused no change in the condition

of the patient. From these observations, it is concluded that the A/G ratio is not the primary factor during this period, but that the albumin is the important factor.

When only small changes in the protein picture are obtained, the results may be of real value only if interpreted with other facts known about the state of the patient and the history of the blood sample.

In such studies, it is important to adhere strictly to a uniform method in the salting out of the albumin if comparable values are to be obtained. Experiments show that the type of filter paper, the size of the filter paper, the size of the sample, and the amount of fluid that passes through the filter paper cause differences in the value of the albumin concentration. However, if enough solution is passed through the filter, all filter papers that we have tested give about the same ultimate value. A standardized procedure should be used throughout a study.

Stimulation With Histamine of Gastric Flow

Leon Schiff, M.D.

The effects of the subcutaneous administration of histamine phosphate on gastric secretion have been studied in one individual for a period of five years. Over 500 fractional aspirations have been carried out under controlled conditions and almost 1,000 injections of the drug (in doses of 0.5 to 1 mg.) have been given. The subject has apparently suffered no systemic harm and has as yet developed no tolerance for the drug.

The subcutaneous administration of histamine produces an increased flow of gastric juice, an increase in the chlorides and free acidity, no constant effect on pepsin, and a relative decrease in fixed base. The total fixed base of gastric juice is apparently not affected, suggesting that the transfer of base from blood plasma to gastric juice is unchanged by histamine.

Twice during the period of study the patient showed achlorhydria which developed without known cause. During one of these phases, the administration of histamine was followed by increase in pepsin, an observation similar to that made by Faber and Holst in cases of pernicious anemia.

The Possibility of Sensitization by Repeated Tuberculin Tests

Waldo E. Nelson, M.D.

An attempt has been made to determine whether repeated intracutaneous injections of tuberculin may cause sensitization in man. Repeated tests have been performed in several groups of childen. In the first group all children who had any reaction whatsoever in either of the first two tests were excluded from subsequent tests. In other groups children who had small, subpositive, or questionable reactions in the first two tests as well as those who had no reaction whatsoever were given repeated injections at varying intervals. Roentgenograms of the chest were taken of most of the children. In all groups there were positive reactors in the third and subsequent tests. It was felt that these reactions were not due to artificially induced tuberculin sensitization for the following reasons:

1. Test 3 was performed 96 hours after test 1, an interval too short to permit induction of sensitization;

2. Failure of consistent response in all groups;

3. Failure to obtain consistent maximum rates or size of reactions in latter tests;

4. Roentgenologic evidence usually accepted as diagnostic of tuberculous lesions in children of all groups who had no or only questionably positive reactions in test 1 or 2.

The Premature Department of the Cincinnati General Hospital

Edward A. Wagner, M.D.

The Premature Department at the Cincinnati General Hospital was briefly described. Admissions per year number approximately one hundred, this year 132.

A special room is maintained at 80 to 85° F. with humidity percentage of 55 to 60. A rigid technic is maintained constantly.

CAUSES OF DEATH IN 25 NECROPSIES	GROUPS IN GRAM WEIGHTS								TOTALS		
	2000+		1500+		1000+		1000-				
	PRIMARY	OTHER	PRIMARY	OTHER	PRIMARY	OTHER	PRIMARY	OTHER	PRIMARY	OTHER	
Prematurity	3	4	2	3	1	1	1	2	7	10	17
Lobular pneumonia	2	1	1	0	1	0	0	0	4	1	5
Lobar pneumonia	0	0	0	0	0	0	0	0	0	0	0
Intracranial hemorrhage (a) Subdural	0	2	1	1	0	1	0	0	1	4	5
(b) Subarachnoid	0	0	2	1	2	0	2	1	6	2	8
(c) Intraventricular	0	0	1	0	1	0	0	0	2	0	2
Atelectasis or incomplete expansion of lungs	0	3	1	3	0	1	1	2	2	9	11
Enteritis	0	2	0	1	0	0	0	0	0	3	3
Patent ductus arteriosus	1	2	0	2	0	2	0	4	1	10	11
Patent foramen ovale	1	2	0	4	0	2	0	3	1	11	12
Syphilitic encephalitis	1	0	0	0	0	0	0	0	1	0	1
Others	0	0	0	4	0	4	0	0	0	14	14
Total primary causes of death									25		

MAY, 1935 TO MAY, 1936	GROUPS IN GRAM WEIGHTS					
	2000+	1500+	1000+	1000-	?	TOTALS
Admissions	40	54	22	8	8	132
Male	21	26	17	3	5	72
Female	19	28	5	5	3	60
White	20	25	17	3	7	72
Black	20	29	5	5	1	60
Members of twin births	5	6	6	4	0	21
Members of triplet births	0	3	1	0	0	4

Feedings are given by medicine dropper, bottle, and gavage at two- or three-hour intervals. Water is given between feedings.

Because of the difficulty encountered in obtaining breast milk, all infants are on a formula of evaporated milk, water, and beta lactose. The results with this feeding compare most favorably with those of the preceding years using breast milk. Peptonization is used in difficult cases.

All infants receive from 10 to 15 c.c. of human blood intramuscularly on admission.

Our greatest problem is the occurrence of diarrhea late in the summer or early fall. Studies have revealed no definite bacteriologic cause.

MAY, 1935 TO MAY, 1936	GROUPS IN GRAM WEIGHTS					
	2000+	1500+	1000+	1000-	?	TOTAL
Number of deaths Total per group	10	20	12	8	8	58
Per cent of deaths—Total per group	25	37	54.5	100	100	43.9
Per cent of recovery	75	63	45.5	—	—	56.1
Number of deaths after 24 hours	7	14	5	—	—	26
Per cent of deaths after 24 hours	18.9	29.2	33.3	—	—	26

TYPE OF DELIVERY	GROUPS IN GRAM WEIGHTS (MAY, 1935, TO MAY, 1936)					
	2000+	1500+	1000+	1000-	?	TOTAL
Breech	1	5	3	0	0	9
Cesarean	1	1	0	0	0	2
Version	0	1	0	0	1	2
Induced	0	0	0	0	0	0
Spontaneous	10	15	3	8	7	43
Unknown	19	29	16	0	0	64
Forceps	9	3	0	0	0	12
Total	40	54	22	8	8	132

	GROUPS IN GRAM WEIGHTS (MAY, 1935, TO MAY, 1936)				
	2000+	1500+	1000+	1000-	?
Average weight on admission—grams	2116	1772	1333.7	827.9	
Average number of days to regain birth weight	12.17	12.45	12.3	00.0	
Average number of days to gain to 2267.5 gr. or 5 lb.	20.7	22.10	22.9	00.0	
Average number of days' residence in hospital	29.16	38.36	34.03	0.658	

	GROUPS IN GRAM WEIGHTS (MAY, 1935, TO MAY, 1936)					
	2000+	1500+	1000+	1000-	?	TOTAL
Positive Wassermann	6	6	0	0	?	12
Negative Wassermann	17	15	5	0	?	37
Unknown Wassermann	20	36	17	8	?	81
Positive mother's Wassermann	5	3	0	0	?	8

The department at the present time is interested in determining the antirachitic value of a lamp with radiations in the 2,800 to 3,200 Angström unit range, and the application of vitamin D to the skin.

PREMATURITY OR IMMATURITY THE CAUSES	GROUPS IN GRAM WEIGHTS				
	2000+	1500+	1000+	1000-	TOTAL
Renal	5	3	0	0	8
Pyelitis	1	4	1	0	6
Eclampsia	2	3	1	1	7
Syphilis	4	1	0	0	5
Induced	3	0	1	1	5
Tuberculosis	2	1	0	0	3
Cardiac condition	0	1	0	1	2
Placenta previa	1	0	1	0	2
Trauma	1	0	0	0	1
Avitaminosis	1	0	0	0	1
Erysipelas	1	0	0	0	1
Multiple pregnancy	4	6	15	0	25
Postoperative	0	1	0	0	1
Pernicious vomiting	1	0	0	0	1
Pneumonia	0	0	0	0	0
Unknown					54
Totals					132

Possible Relation of Bacillus Coli to Acute Enteritis in Infants

Merlin L. Cooper, M.D.

Many infants develop a severe acute enteritis in Cincinnati every summer between July and November. The clinical signs and symptoms are much the same in all. There is no consistency in the types of bacteria found in the stool cultures. Patients with almost identical clinical findings may have entirely different bacteria in their stools with the exception of *B. coli*. This organism, *B. coli*, is the only type found in the intestinal tracts of all the patients. We wondered if this organism might play any part in the intestinal disturbances of these infants. A number of cultures of *B. coli* from stools were studied. All were found to produce a toxic substance in broth media which withstood heating at 100° C. for one hour. Injection of this heated toxic substance intravenously into rabbits produced no symptoms for 30 to 45 minutes. The animals then became restless, the conjunctivae became injected, and there was weeping from the eyes. The respiration became very rapid and deep. There was fever and death generally occurred after one and a half to three hours. Necropsy studies revealed intensely swollen congested livers. Microscopic studies of sections of various organs revealed acute congestion, fatty infiltration, and cloudy swelling of the liver; acute congestion, atelectasis, extravasation of red blood cells into the alveoli and edema of the interstitial tissue of the lungs; acute congestion, toxic changes, and edema of the spleen. The quantity of toxic substance varied with different types of media and various peptones and length of incubation. Filtration of the toxic substance through a collodion membrane gave a protein-free filtrate without any reduction in toxicity for rabbits. Attempts to immunize rabbits with the toxic filtrate failed to immunize to the toxic substance but did immunize to the bacteria. This is a preliminary report of studies still in progress.

Pleurodynia

Barbara Hewell, M.D.

The paper presents the clinical and bacteriologic findings on 70 children with epidemic pleurodynia, studied in the Children's Hospital in the summer of 1935. Eighty-five per cent of the patients were under ten years of age.

The characteristic picture was the sudden onset of pain, usually abdominal, with fever, and the tendency to recurrence of pain and fever on the third or fourth day of the illness. The onset was accompanied by nausea in 35 per cent, by vomiting in 31 per cent, and chills in 12 per cent. Other findings were headache in 42 per cent, constipation in 36 per cent, nasal discharge in 25 per cent, pharyngitis in 25 per cent, sore throat in 15 per cent, and back pain in 11 per cent. X-ray films of the chest were negative in 40 patients. Fourteen spinal punctures were also negative. Hemoglobin and erythrocyte values were normal. The leucocyte counts tended to be normal or relatively low and the differential count within normal limits.

Twenty-six of the most typical cases were studied bacteriologically; 25 blood cultures and 3 spinal fluid cultures remained negative for from five to six weeks; throat cultures from 22 patients and nasal washings from 8 patients showed consistently a green-producing, very slightly hemolytic streptococcus, growing in tiny colonies; 11 stool cultures were not remarkable.

Fifty-four animals were injected with material and cultures from these patients. Nineteen animals died, and 16 autopsies were performed. The lungs showed congestion, edema, and some acute cellular reaction. The studies were suggestive of the presence of a filtrable virus and will be reported in detail in a later paper.

Pellagra in Children and the Present Status of Pellagra

Tom Spies, M.D.

In a series of fifty cases of endemic pellagra treated in Birmingham, Ala., early in 1936, three were children under thirteen years of age. The youngest was two and one-half years.

The history is usually that of an inadequate or unbalanced diet, and physical examination shows characteristic pellagrous dermal and lingual lesions. Since there are no specific laboratory tests for this disease, atypical cases are often difficult to recognize.

Pellagra at any age is a serious disease unless prompt, intensive, and persistent treatment is given. The essence of treatment is the administration of a high caloric, well-balanced diet, large amounts of powdered brewers' yeast, adequate rest, and proper nursing care. The disease can usually be prevented if careful attention is paid to the diets of people with organic disease, those who are poor, and those with improper dietary habits.

The Vitamin D Content of Blood Serum

Josef Warkany, M.D.

A direct estimation of the vitamin D content of blood serum necessary to produce healing in rachitic rats has been described in detail recently. It was first necessary to determine whether the vitamin D content of the blood serum is a more or less constant factor. As soon as this was accomplished, an attempt was made to find out whether this level could be changed under abnormal conditions. By means of quantitative tests in animals, it was shown that the vitamin D level in the blood serum may be increased and by oral administration of viosterol may be raised to 1,000 times the normal level.

Estimations of the vitamin D level in the blood serum of the human organism were performed, and the average figures were presented. A comparison of the vitamin D levels of white and colored children living under the same conditions was made and the effect of irradiation on both groups observed.

Finally, several pathologic cases in which estimations of the vitamin D level in the blood serum were found valuable in the diagnosis and treatment were reported.

The Rôle of the Liver in the Development of Ketosis in Children

I. Arthur Mirsky

Our data reveal the following:

1. The liver is the main, if not the only, site of ketone body formation; the muscles do not contribute to this process.

2. The production of ketone bodies by the liver is usually associated with a depletion of liver glycogen so that there is a diminution in the carbohydrate available for utilization by that orgnn.

3. The liver does not utilize ketone bodies whereas the muscles do, thus indicating that the oxidation of fat never goes beyond the stage of ketone bodies in the liver.

4. Any process which will provide the liver with adequate amounts of available glycogen will inhibit the formation of ketone bodies. This occurs even in the complete absence of insulin when glucose is injected in amounts sufficient to cause a deposition of glycogen in the liver.

5. An increase in metabolic rate is associated with an increase in carbohydrate utilization by the extrahepatic tissues and a consequent decrease in liver glycogen.

These and other data have led to the tentative hypothesis that the liver preferentially burns carbohydrate, but, when the latter is not available, fat and protein are oxidized. When this occurs, ketone bodies, as end products of fat metabolism in the liver, are secreted into the blood stream and utilized by the extrahepatic tissues. Clinical ketosis will depend upon the difference between the rate of formation and the rate of utilization of these substances.

Since the metabolic rate of the infant or child is relatively higher than that of the adult, the extrahepatic tissues of the former utilize carbohydrate at a relatively greater rate than that of the latter. Hence, a more rapid depletion of liver glycogen can occur in the child. Any insult which tends to reduce the liver glycogen in the adult will produce a more rapid diminution in the child, and consequently the latter exhibits a greater susceptibility to ketosis. Thus, all conditions which are associated with ketosis in the child can be attributed to a depletion of liver glycogen. The only exception is the occurrence of ketosis in von Gierke's disease, but in that instance the liver glycogen is fixed and is not available for utilization.

A Case of Congenital Heart Disease With a Familial History

Robert H. Kotte, M.D.

This family is interesting for the unusual combination of abnormalities. A little girl, the second child in a family of three children, had congenital heart disease. The symptoms, physical findings, x-ray, electrocardiographic, and blood examinations are those of the tetralogy of Fallot. A younger brother had hypospadias. The father and paternal grandfather have marked clubbing of the fingers and toes characteristic of hypertrophic osteo-arthropathy. There was no history of a severe illness or any chronic heart or pulmonary disease or any evidence on physical examination, x-ray, electrocardiographic and blood examinations, and vital capacity tests to account for the abnormality.

A Simple Technic for Determination of Blood Grouping and Compatibility From Small Amounts of Defibrinated Whole Blood

Paul Hoxworth, M.D., and Azel Ames, M.D.

A technic, combining the principles of the Vincent open macroscopic methods for blood grouping and the Coca compatibility test for direct matching, is described, and the rationale of these methods is presented. Each method has been slightly modified so that both determinations may be made with a single small sample of

defibrinated whole blood. The adoption of these methods at the Cincinnati General Hospital has been the result of a gradual evolution toward a more efficient routine for the selection of donors from groups of unknown volunteers.

For purposes of contrast, brief reference is made to the methods used by us in the past. The results of examinations made in a parallel series on more than 200 consecutive specimens of blood using both the former methods and the Vincent-Coca method are given. The advantages of the Vincent and the Coca procedures in general, and the combined technic in particular, are discussed. The application of the Coca compatibility test to the discrimination between high and low titered "universal" donors is stressed.

The importance of employing high titered test serums for use in the Vincent method is emphasized. Special emphasis is placed on the necessity for the use of serums of high agglutinin titer in determining the blood groups of children. The preparation of an abundant supply of such serums for our own use is reported.

Report of an Unusual Condition Involving the Bones in a Ten-Year-Old Boy

Leo S. Friedman, M.D.

C. S., a white male, aged ten years, was admitted to the hospital Aug. 21, 1936. The family history was negative, the birth normal. For approximately one year the patient had complained of pains in the bones and joints, especially those of the lower extremities. Fever was present at times. Three months before admission, he developed swelling of the knees and ankles and subsequently of the fingers and elbows.

Physical examination revealed a very thin, weak, pale boy with swelling and tenderness about the right index finger, knees, and ankles, with pain on motion. The liver and the spleen and the lymph nodes were not enlarged. The temperature was 103° F. The laboratory examination showed hemoglobin 47 per cent, white blood cells, 6,650; red blood cells, 3,500,000; polymorphonuclear leucocytes, 64 per cent; eosinophiles, 4 per cent; marked poikilocytosis and anisocytosis with polychromatophilia. Roentgenograms of all the bones revealed compression and narrowing of the vertebral bodies, especially in the lumbar region, and decalcification in the ends of the diaphyses of the humerus, radii, phalanges, femurs, and tibiae. The epiphyses were normal. The tibiae showed evidence of periostitis. The skull bones and sella turcica were normal. In spite of repeated transfusions, the blood showed a marked tendency to a decreased red count and hemoglobin, with a leucopenia as low as 1,700, and a gradually increasing number of immature white cells. A biopsy of the sternum was variously interpreted as fibrosarcoma, neuroblastoma, and leucemia with most of the evidence in favor of the last diagnosis. The boy has had pathologic separation of the heads of the humerus and the femur on the right side. The fever varies from normal to 105° F. Recently there has been slight enlargement of the right inguinal nodes.

A Case of Unilateral Communicating Hydrocephalus Improved by Ureterodural Anastomosis

J. Victor Greenebaum, M.D., and Henry B. Freiberg, M.D.

This child, a boy six years of age, has been under observation since 1933. The history of his illness dates back to June, 1930, when at the age of twelve months he had an attack of fever with severe convulsions of the right side of the body and was ill for three weeks. The diagnosis of encephalitis was made at that time. Since that illness the convulsions occurred daily. There was inability to talk, and contractures of the right leg and arm developed. A diagnostic study at the Jewish Hospital including an encephalogram and a spinal puncture which were performed by Dr. Samuel Zielonka, showed the left ventricle markedly dilated with moderate

atrophy of the cortex and slight dilatation of the right ventricle. Further studies proved this to be a communicating type of hydrocephalus. In order to provide drainage, a glass tube was inserted into the ventricle which allowed the cerebral fluid to drain beneath the scalp. This was performed in April, 1934.

It was necessary to remove the tube in February, 1935. Convulsions which had been relieved by the above procedure recurred after its removal. The child was returned to the Jewish Hospital again where Dr. Henry B. Freiberg and Dr. Louis A. Lurie suggested a more radical type of treatment, namely, a ureterodural anastomosis. The parents agreed to permit the operation in spite of the risk involved. The operation was performed in two stages by Dr. Henry Freiberg and Dr. Samuel Zielonka.

The technic of which is as follows:

Unlike similar previous operations it was thought wise to do this procedure in two stages, the first stage consisting of removal of the kidney and the dissection of the ureter and kidney pelvis from within the kidney. Through a stab wound in the lumbar group of muscles, the ureter was brought beneath the skin of the back in the region of the third lumbar vertebra, and there it was attached, all wounds being closed in the usual way. Two weeks later an incision was made over the lumbar spinal region, the ureter previously imbedded in that position was isolated, and the dura exposed. An anastomosis was made between the ureter, which in reality was the kidney pelvis, and the dura, care being exercised also to open and include in the suture the arachnoid. The wound was closed over this anastomosis without drainage. The postoperative course was stormy, but the patient recovered. The patient steadily improved and had no further convulsions. It was possible to teach him a few things, such as the position of his eyes, ears, nose, and mouth, and other parts of his body. Subsequent studies seem to point to the fact that the ureter is still patent and the anastomosis is intact.

Experience With Joint Fusions in Children

Albert H. Freiberg, M.D.

The results of fusion in tuberculosis of joints in children have been highly satisfactory when a proper selection of cases has been made and the proper time has been chosen for doing them. Poliomyelitis furnishes the ground for the performance of many other joint fusions in children. The unsatisfactory outcome of many muscle transplantations, particularly in the foot, caused Hoke to advocate fusion of the subastragalar joint in order to accomplish stabilization which seemed otherwise impracticable. The success of such operations, either with or without accompanying transplantation, has caused them to become very widely practiced, and they have become standard procedures, modified in one way or another. However, in the case of structural scoliosis produced by poliomyelitis, we have a situation which has defied nonoperative treatment with great frequency. Notwithstanding continuous recumbency this deformity often proceeds unchecked, and it is hoped that for these cases we have found real help in spinal fusion. For the most part, we have been doing them under local anesthesia with great satisfaction.

Demonstration of typical cases followed.

Antiserum Intradermal Reactions in the Diagnosis of Certain Infectious Diseases

Lee Foshay, M.D.

Intradermal injections of specific antiserums into patients with homologous infections provoke characteristic bacterial-specific responses. Normal serums and heterologous immune serums as simultaneous controls fail to do this. When initial symptoms are accompanied by bacteremias, positive reactions are obtainable as early

as eight hours thereafter. Only rarely will the tests fail to betray the nature of the infecting agent within the first four or five days of the disease. Against standard diagnostic procedures these tests showed an almost perfect correlation in 1,055 patients tested.

For tularemia, it is demonstrated that positive responses depend upon an antigen-antibody reaction which involves only the bacterial species-specific polysaccharide. Carbohydrate antigen is elaborated by the infecting bacteria and is present in the skin of the patient. Carbohydrate antibody is in the specific antiserum.

It is believed the same mechanism holds for other bacterial diseases and for one virus disease (lymphogranuloma inguinale). As that fraction of the invading living antigen being tested for is the component which confers species or strain specificity to the microorganism itself, the reaction is a diagnostic test of very great precision and accuracy. Its limitations and certain other uses will be indicated.

The Relation of Endocrine Disorders to Hereditary Deviations

A. Graeme Mitchell, M.D., and Josef Warkany, M.D.

The difficulty of applying new discoveries in the field of endocrine physiology to clinical material lies partly in the fact that subjects with endocrine disturbances often have independent coordinated defects. These symptoms may be misinterpreted as the cause of an endocrine defect, or the endocrine defect may be incorrectly considered the cause of such coordinated symptoms. A third possibility is that a causal connection may be assumed between two independent endocrine diseases found in one subject. For all of these possibilities examples were cited.

The establishment of syndromes of so-called degenerative deviations on the basis of a small number of observations and the dangers of this were discussed, and the application of statistical methods of these observations in order to ascertain the true frequency of such association of symptoms was recommended.

Emphasis was placed on the fact that a thorough investigation of the familial background of the subject is often enlightening, since endocrine disturbances and symptoms found simultaneously in the individual may be dissociated in other members of the family, thus proving that one sign or symptom cannot be the cause of the other.

News and Notes

The **American Board of Pediatrics** announces examinations in connection with the following meetings:

Los Angeles, Calif.—During the meeting of Region IV of the American Academy of Pediatrics in the latter part of October, 1937.

Chicago, Ill.—During the meeting of Region III of the American Academy of Pediatrics, November 4, 5, and 6, 1937.

Boston, Mass.—During the meeting of Region I of the American Academy of Pediatrics, November 12 and 13, 1937.

New Orleans, La.—During the joint meeting of Region II of the American Academy of Pediatrics and the Southern Medical Association, Nov. 30, Dec. 1, 2, and 3, 1937.

Definite dates for the examinations will be published later.

The following physicians have been certified by the **American Board of Pediatrics** since the last report:

William Bradford Adams, Springfield, Mass.
Ben Benjamin, Montreal, Canada
Claude McKinley Burpee, Augusta, Ga.
Iris M. Chamberlain, Chicago, Ill.
Forris Ensor Chick, New York, N. Y.
Harry Eron Cohen, New York, N. Y.
Walter R. Coles, Brooklyn, N. Y.
Reuben Arthur Craig, Kokomo, Ind.
Hugh Jefferson Davis, Washington, D. C.
William E. Donahoe, Sioux Falls, S. D.
Louis M. Earle, Hollywood, Calif.
George H. Garrison, Oklahoma City, Okla.
George Ketcham Hagaman, St. Paul, Minn.
Lawrence Vance Hanlon, Brooklyn, N. Y.
Henry P. Harrell, Augusta, Ga.
Norman Louis Hawkins, Watertown, N. Y.
F. G. Hedenstrom, St. Paul, Minn.
Julius Heilbrunn, Jersey City, N. J.
Lewis D. Hoppe, Jr., Atlanta, Ga.
John Taylor Howell, Jr., New York, N. Y.
Francis Rush Janney, Wauwatosa, Wis.
Newell Jones, Hollywood, Calif.
J. N. Lande, Sioux City, Iowa
John Fitch Landon, New York, N. Y.
Richard A. Lawrence, Albany, N. Y.
Abel Lax, Montreal, Canada
William Ray Little, Trenton, N. J.
Norman M. Mac Neill, Philadelphia, Pa.
Thomas Juett Marshall, Paducah, Ky.
William Charles McGuire, New Haven, Conn.
William Baird McIlwaine, Petersburg, Va.
John M. Mitchell, Evanston, Ill.
Oscar A. Mockridge, Montclair, N. J.
Fred Moore, Des Moines, Iowa
Harrold A. Murray, Newark, N. J.
Kenneth D. Nichol, Brooklyn, N. Y.
Roland Edward Nutting, Duluth, Minn.
Thomas E. Oast, Portsmouth, Va.
William Francis O'Donnell, Washington, D. C.
Lawrence Francis Richdorf, Minneapolis, Minn.
William Rosenson, New York, N. Y.
Joseph Carr Savage, Los Angeles, Calif.
R. Hunter Scott, Newark, N. J.
Harry A. Spigel, Washington, D. C.
Frank E. Stevenson, Cincinnati, Ohio
Alexander Stewart, St. Paul, Minn.
Lucy Porter Sutton, New York, N. Y.
Edward Sheppard Thorpe, Jr., Philadelphia, Pa.
Harmon Tremaine, Boise, Idaho
Thomas Edward Waldie, New York, N. Y.
Walter F. Watton, Brooklyn, N. Y.
Robert Lawson Wilder, Minneapolis, Minn.
LeRoy A. Wilkes, Trenton, N. J.
James R. Wilson, Syracuse, N. Y.

On the last list, the address of Dr. Saul Schlegman was given as White Plains, Ill., and should have been White Plains, N. Y.

Academy News

Final notice is given of the seventh annual meeting of the American Academy of Pediatrics to be held on June 3, 4, and 5, 1937, in New York City, under the presidency of Dr. Laurence R. DeBuys. Headquarters for the meeting will be at the Waldorf-Astoria Hotel. This meeting precedes that of the American Medical Association by several days.